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# TRANSIENT AURICULOVENTRICULAR DISSOCIATION WITH VARYING VENTRICULAR COMPLEXES CAUSED BY DIGITALIS *

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In 1913, Cohn[1] and Oppenheimer and Williams[2] described cases of heart-block in which the form of the ventricular complex showed frequent change.

In Cohn's case the heart-block was transient. On Aug. 22, 1910, the patient showed partial heart-block with a 3-2 rhythm as shown by polygraphic tracings. On Feb. 10, 1911, this patient was studied again and showed a partial heart-block with a 2-1 rhythm. On February 11 and 13 there was a complete auriculoventricular dissociation. At this time electrocardiographic tracings were made and it was found that successive ventricular complexes changed their outline so that no two were precisely alike. Two general types, however, could be distinguished, the one resembling the type of beat arising from stimuli originating in the wall of the right ventricle and the other those arising in the wall of the left ventricle. Gradual variations were made out between these two types. With the change in type there was also a change in interval between successive ventricular complexes. This dissociation did not persist, for shortly after this time the rhythm was restored to a normal one. Later examinations on Dec. 19, 1911, and Feb. 18, 1913, showed that the normal rhythm had been maintained except for an occasional premature ventricular contraction.

This was a patient with cardiac decompensation, the etiology of which is not clear from the history. It appears to have been a slowly developing myocardial insufficiency. It seems not unlikely that the heart-block observed at the various times was the result of digitalis therapy.

In the case of Oppenheimer and Williams the heart-block was permanent during the period of observation from Feb. 26, 1912, to the day of the patient's death, Dec. 31, 1912. Histologic examination of the heart, however, revealed no organic lesion to account for the

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1. Cohn: Heart, 1913, v, 5.
2. Oppenheimer and Williams: Proc. Soc. Exper. Biol. and Med., 1913, x, 86.

block in the auriculonodal junction, the node of Tawara or the main stem and its branches. The nodal artery was sclerotic. The variations in the ventricular complexes were seen not only from one examination to the next but often from beat to beat. The waves Q, R, S and T all showed variations; for example in Leads 1 and 2 the R waves were sometimes upright and sometimes inverted. In Lead 3 the wave R was always inverted. The patient had marked Cheyne-Stokes respiration and the auricular rate was strikingly reduced during the dyspneic period, while the ventricular rate showed little change.

CASE 1.—The patient was in the Peter Bent Brigham Hospital on two occasions; the first time (Peter Bent Brigham Hospital Medical No. 426) from Oct. 18 to Dec. 18, 1913; the second time (Peter Bent Brigham Hospital Medical No. 939) from March 11 to April 5, 1914, on which day he died.

Fig. 1, Case 1.—Lead I, taken March 20, 1914.

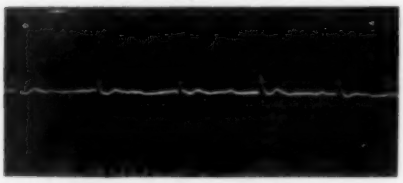

Fig. 2, Case 1.—Lead I, taken after Figure 1, March 20, 1914.

The patient, a man aged 48, had been somewhat short of breath for the past two or three years, but not enough to keep him from his work, that of a barber. He had had more or less swelling of his ankles for ten years. During the winter prior to admission he had a chronic cough. About two months before admission he noticed that he was sleeping poorly and shortly after this his breath became very short, particularly at night, so that he was obliged to sleep sitting propped upright in bed. When he first entered the hospital the right border of cardiac dulness was at the right sternal margin; the left border 9 cm. to the left of the midsternum. The apex beat was not seen or felt. Cardiac sounds were distant and a faint, blowing systolic murmur was heard, loudest at the apex. There were four or five beats of the same length followed by an extra beat, evidently an extra systole. The abdominal wall was edematous and brawny without shifting dulness. There was a brawny edema of the arms and legs.

The patient responded well to digitalis, and had a marked diuresis with disappearance of his edema. There was considerable evidence that in addition

to cardiac decompensation the patient had hypothyroidism. With thyroid extract in addition to cardiac therapy he improved markedly and left the hospital Dec. 18, 1913, in good condition, though unable to undergo much exertion.

After leaving the hospital the patient remained at home on account of weakness and shortness of breath. After a short time he became again very dyspneic and orthopneic, especially at night. He had considerable cough and raised a small amount of frothy sputum. Late in February, 1914, his feet began to swell. About the middle of April his abdomen became prominent. Symptoms of cardiac decompensation increased until he was readmitted on March 11, 1914, in an almost pulseless state.

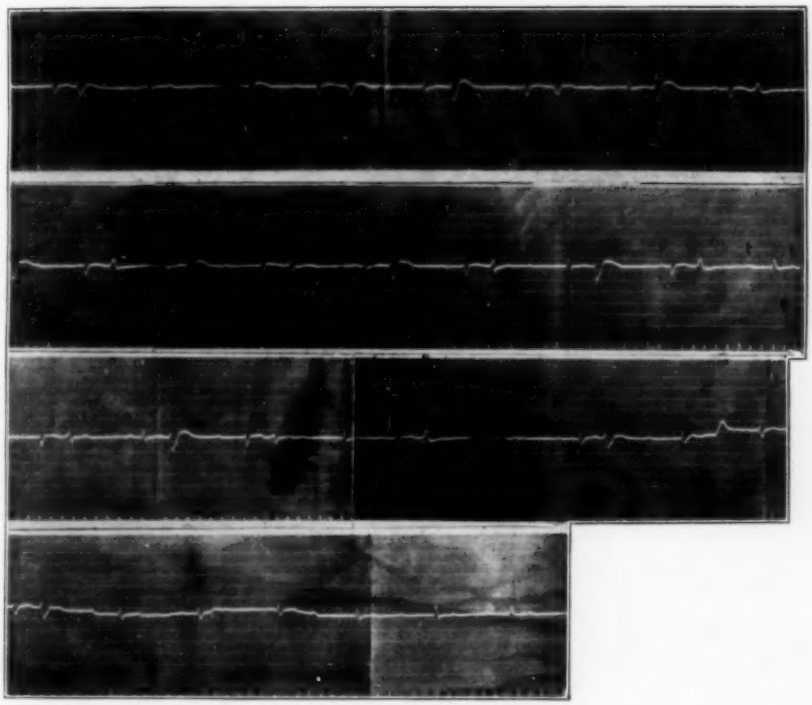

Fig. 3, Case 1.—Lead I, March 21, 1914. The strips form a continuous record.

On March 11 physical examination showed the patient lying propped up in bed, moderately dyspneic and cyanotic with moderate edema of the legs below the knees and moderate edema of the abdominal wall and of the thorax as high up as the nipples. The apex beat of the heart could not be felt. The borders of cardiac dulness were made out with great difficulty owing to hyperresonance of the chest. Heart sounds at the apex were barely audible; at the base the sounds were a little more distinct but were heard with great difficulty. No murmurs were heard. The heart action was regular. No pulse could be made out at the wrist. The lungs showed dulness at both bases with a few moist râles. The abdomen showed shifting dulness. The liver was enlarged, tender and pulsating. On March 12 the patient had gradually

improved, his respiration had become Cheyne-Stokes in type but he was less dyspneic. On March 14 the patient had improved further and there had been marked diuresis with appreciable diminution of the edema of the extremities and the ascites. The heart sounds were stronger; still there was no murmur. On March 17 a systolic murmur was heard over the whole precordium. By April 2 the patient's condition had grown less good. He seemed stuporous. There was marked Cheyne-Stokes respiration. On April 4 he had grown distinctly worse and on April 5 he continued to fail and died at 4:45 a. m. The cardiac condition had been regarded as one of chronic myocarditis in an individual with moderate hypothyroidism and moderate chronic nephritis.

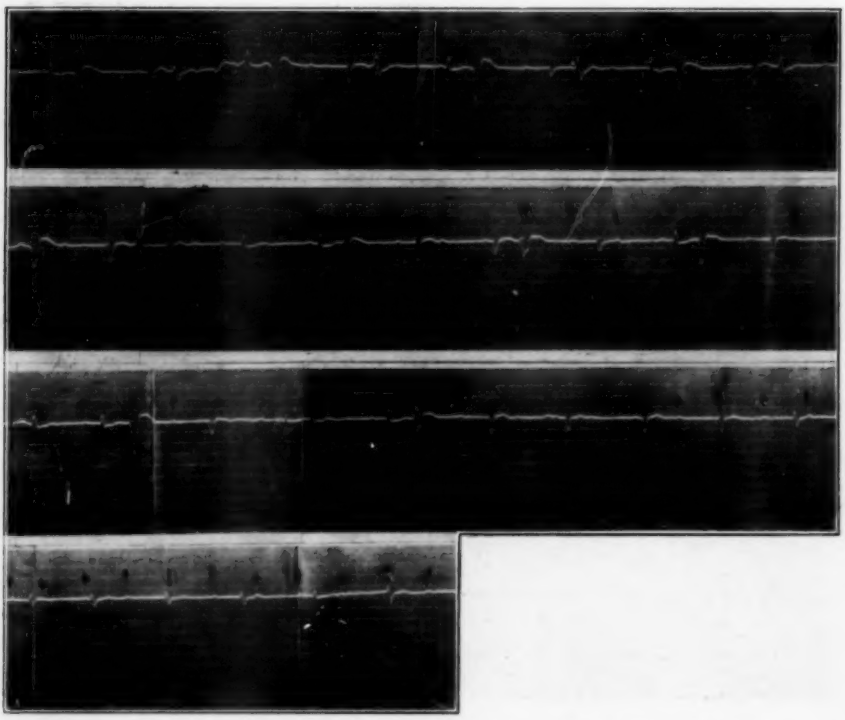

Fig. 4, Case 1.—Lead II, March 21, 1914. The strips form a continuous record.

During the second period in the hospital electrocardiographic studies were made. Some electrocardiograms taken on March 20 showed complete dissociation[3] with an auricular rate of 78, a ventricular rate of 66, with paired ventricular beats coming in quite a regular relation to each other (Fig. 1), the first one of the pair appearing to have its origin in the bundle of His, and the

3. In these cases the curves have been interpreted as showing complete dissociation. They might be interpreted instead as partial block with "P" waves at times in close association with ventricular complexes because contractions originating below the auricles have stimulated auricular contractions instead of the auricles and ventricles beating entirely independently of each other.

second one to have its origin in the ventricle. This condition, however, did not persist constantly, inasmuch as in some leads there was no pairing of beats in a regular sequence, while in others (Fig. 2), both auricular and ventricular rates were quite regular though completely dissociated and all ventricular complexes were of supraventricular origin.

On the next day, March 21, the same general appearance persisted (Figs. 3, 4 and 5) though there was greater variation in the form of the various ventricular complexes. There was a distinct tendency to an alternation of the character of the paired beats, in which the first ventricular complex of the

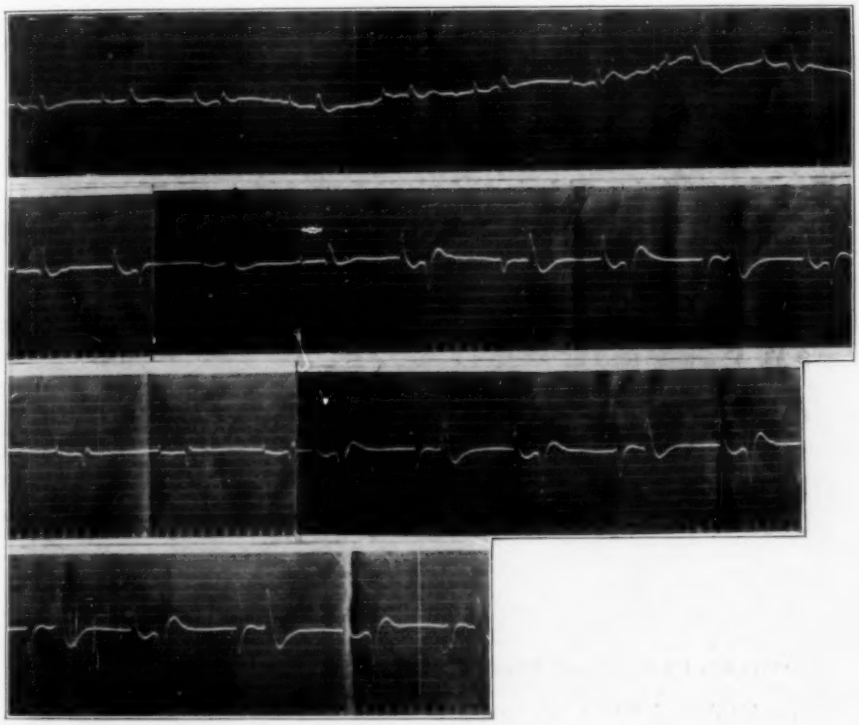

Fig. 5, Case 1.—Lead III, March 21, 1914. The strips form a continuous record except for a short break in the third strip.

pair gave an upward curve, and the second one a downward curve, and this arrangement changed in the next group so that the first complex was down and the second one up, and there was a considerable tendency to a regular alternation in this arrangement. In addition there were frequent minor changes in ventricular complexes as they succeeded each other, so that a great variety of complexes appear in any given curve.

The curve taken on March 25 showed a perfectly regular rate of 90, with all impulses transmitted from auricle to ventricle and ventricular complexes of normal form. There was a considerable delay, however, in the "P-R" interval, which reached its maximum on the next day, March 26, and then gradually

decreased, though never came quite to the normal time of transmission. The heart rate increased to 90 on March 26, to 104 on March 27, to 108 on March 28, and to 120 on March 30, and with this increase in rate of contractions the heart remained regular, the complexes normal in form, but the "T" and "P" waves gradually approached nearer and nearer until they became superimposed, which feature was very well shown by some curves taken on March 30, in which, following vagus irritation, there were some greatly increased intervals between successive "R" waves, and during these the "T" and "P" waves became separated (Fig. 6).

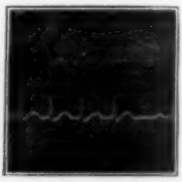

Fig. 6, Case 1.—Lead II, March 30, 1914. Curve shows a pause caused by vagus pressure.

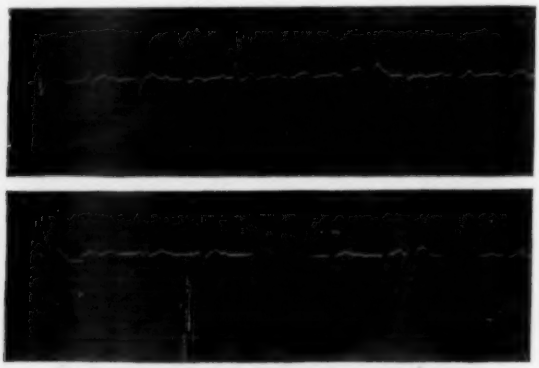

Fig. 7, Case 1.—Lead I, April 3, 1914. The two strips form a continuous curve and the second one is continuous with the curve in Figure 8.

On April 2, though still regular, the rate of the heart slowed down to 84, and the "P-R" interval increased slightly in length.

On April 3 heart-block again occurred with an auricular rate of 126 and a ventricular rate of 72. In Lead 1 (Figs. 7 and 8) this was present throughout, and at times there was such a pairing of the ventricular beats and changes in ventricular complexes as occurred when the heart was previously in block on March 20 and 21. This block, however, was not maintained, because in the interval between taking Lead 1 and Lead 2 the ventricular rate increased to 120, the ventricular complexes became normal in form, the "T" and "P" waves coincided (Fig. 9). This condition persisted while Lead 3 was being taken. After Lead 3 was taken, Lead 1 was again taken, and at this time there was an auricular rate of 120 and a ventricular rate of 60, a partial heart-block with 2-1 rhythm. There was a "P-R" interval when transmission was not blocked varying between 0.2 and 0.24 of a second.

April 4 electrocardiograms showed a rate of 120 in Lead 1 with a superimposed "P" and "T" wave, and a "P-R" interval of 0.24 to 0.28 of a second. At one point in this curve there was a blocked auriculoventricular transmission and a pause of about double the length of the preceding intervals between "R" waves. Lead 2 on April 4 showed no blocking, whereas Lead 3 (Fig. 10) showed a complete block and an auricular rate of 120 and a ventricular rate of 60. This apparently was not a partial block but a complete one, notwithstanding the fact that the auricular rate is twice that of the ventricular. This is brought out by the great variation in the time interval between the beginning of the "P" wave and the beginning of the next following "R" wave. At first glance, however, it would seem to be a partial block, with a 2 - 1 rhythm, the first beat not followed by a ventricular contraction, and the second beat fol-

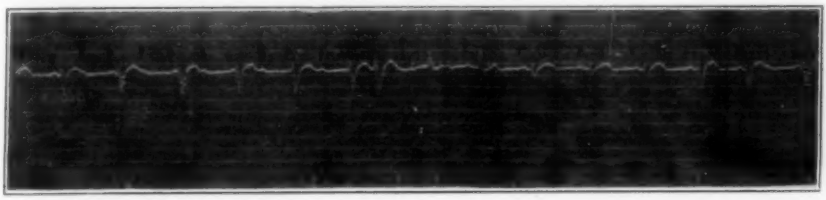

Fig. 8, Case 1.—Lead I, April 3, 1914. This strip is continuous with the second strip in Figure 7.

lowed by a ventricular contraction. Here again changes in form of ventricular complexes occur. A little later another tracing was taken which in Lead 1 shows a ventricular rate of 66 with an apparent complete block; however, the "P" waves are not distinct enough to justify any definite statement. Leads 2 and 3 have an auricular rate of 114 and a ventricular rate of 72. The complete blocking is much more evident as shown by the variations in conduction time.

The patient died during the night following these last tracings and at necropsy the heart showed the following condition:

Fig. 9, Case 1.—Lead II, April 3, 1914. Curve taken almost immediately following that shown in Figure 8.

Heart: Weight, 560 gm. In situ the heart borders measured 5 cm. to the right and 11 cm. to the left (horizontal measurements) of the midline. The right auricle was slightly dilated. The appendages were free. The pericardium was everywhere glistening. The tricuspid valve measured 12.5 cm. The line of closure of valves showed no abnormalties; the valves everywhere were delicate. The chordae tendineae were not thickened. There was slight dilatation of the right ventricle and the endocardial surface was everywhere glistening, showing no abnormalities. The wall measured 6 mm. The pulmonary valve measured 8.5 cm., the semilunar cusps were normal; the line of closure of cusps showed no roughening. The pulmonary artery was incised in situ; it showed no clots. There was a small amount of clot in the chambers above

described. The left auricle was not dilated. The auricular appendage contained a small irregular mass of fibrinous material, very fragile; this was somewhat whiter than normal but apparently was clot. The mitral valve measured 11.65 cm. The valve was thickened throughout. The chordae tendineae were somewhat thickened. There was no apparent change along the line of closure though superficially it was roughened. The wall of the left ventricle measured 1.6 cm. In the region of the septum, about 4 cm. below the aortic valve, was a mass which extended down to the apex, it being 4 cm. in length, adherent to the endocardium, irregular in outline, reddish in color and covered by a definite thin whitish membrane. The heart muscle was dark red in color, was of fairly good firmness; on cross section it was homogeneous and did not show macroscopic

Fig. 10, Case 1.—Lead III, April 4, 1914.

increase in connective-tissue elements. There was definite thickening of the endocardium, especially of the left auricle.

Coronary arteries: The orifices were open. There was marked thickening of the walls of the vessels; this was most marked down to the level of the bifurcation of the transverse and descending branches. In portions the lumen was practically obliterated. The walls were firm but not brittle. In one portion of the left anterior coronary there was apparently total obliteration of the lumen. Sections of heart muscle taken for microscopic study showed no interstitial fibrosis. There was no evident lesion of the conduction system.

Case 2.—In this case the patient was in the Peter Bent Brigham Hospital (Medical No. 1717) from Oct. 3, 1914, to Nov. 29, 1914, on which day she died. The patient was a woman, aged 29, who about seven months before admission, while in the seventh month of pregnancy, began to be troubled with

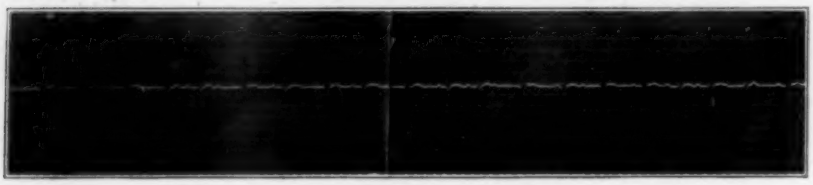

Fig. 11, Case 2.—Lead I, Nov. 23, 1914, 9:25 a. m.

shortness of breath and soon became unable to lie down flat on account of dyspnea. About three weeks after this onset she went into labor and was delivered of a stillborn child. After remaining in bed for two weeks she got up and went about her work though she felt very weak. One month later she developed bronchitis attended with cough and expectoration, at times blood tinged. She began to have palpitation about three months before she came to the hospital and her feet began to swell, the swelling gradually extending up her legs. About three weeks before admission the swelling had involved her abdomen. Notwithstanding these symptoms she had remained up doing her housework as best she could.

When she entered the hospital, Oct. 3, 1914, she was moderately dyspneic and her lips and skin were somewhat cyanotic. She had marked edema of the legs, moderate edema of her forearms, marked edema of her abdominal wall and the lower part of the thorax. Her abdomen contained fluid. There appeared also to be a moderate amount of fluid in each thoracic cavity. The right border of cardiac dulness was 5 cm. to the right of the midsternal line; the left border 16 cm. to the left of the midsternal line. The heart action was rapid and regular with a distinct presystolic gallop rhythm over the base, There was a short systolic murmur heard in the apex region. The pulmonic second sound was markedly accentuated. The systolic murmur present on admission at times disappeared, though it was usually present. Her condition grad-

Fig. 12, Case 2.——Lead II, Nov. 23, 1914. Record taken very shortly after that shown in Figure 11.

ually improved, then remained stationary with a varying amount of edema. She received digitalis from time to time with no very marked effect on cardiac rate or rhythm except in the period beginning on November 22 in the afternoon. Up to the day of her death her general condition had not very essentially changed from that at the time of her admission. On November 29 she appeared as usual sitting propped up in bed, and was brightly talking to her neighbors when she suddenly died. We had considered the condition clinically as chronic myocarditis. No necropsy could be obtained.

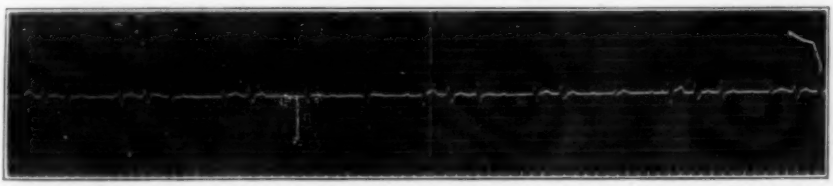

Fig. 13, Case 2.—Lead I, Nov. 23, 1914, 9:45 a. m.

During her stay in the hospital electrocardiographic studies were made. From October 4 to November 22 numerous electrocardiograms showed essentially the same type of tracing with a "P - R" interval of about 0.16 of a second and normal except for a contour of ventricular complexes indicating a moderate degree of right ventricular hypertrophy. During all this period the patient had taken a considerable amount of digitalis as mentioned above, without any very definite effect of any kind except occasional nausea, at which time the digitalis was stopped.

On November 22 after having been on 10 c.c. of an infusion of digitalis three times a day from November 11 to 16, and four times a day from November 16 to 21, on which day the dose was increased in the afternoon to 12 c.c. four times a day, the patient became nauseated at 4:30 p. m., and the digitalis was omitted.

Electrocardiograms were taken on the morning of November 22 and were similar to those taken on the preceding days. That afternoon the pulse fell from 110 to 90 and in the evening to 60, which was its rate next morning, November 23. An electrocardiogram was taken at 9:15 a. m. November 23, and showed at this time a rate of 93 with a long "P - R" interval, at times 0.34 of a second, in Lead 1. In Lead 2, taken a short time after Lead 1, the "P - R" interval had decreased to 0.22 of a second in the first part of the lead. In the latter part of the curve it lengthened out and there was a blocked impulse followed by two ectopic ventricular beats with blunt notched downward waves. In Lead 3 conduction time was similar to the first part of Lead 2. Ten minutes later there was complete auriculoventricular dissociation with an auricular rate

Fig. 14, Case 2.—Lead III, Nov. 23, 1914. Record taken shortly after that shown in Figure 13.

of about 99 and a ventricular rate of about 70. In Lead 1 (Fig. 11), succeeding ventricular complexes showed a change from complex to complex with two general types of waves; one with a moderately high "R" wave and a very slight "S" wave; the other with a slightly higher "R" wave and an "S" wave nearly as great as the "R" wave. In Lead 2 (Fig. 12) there appeared with persisting complete dissociation a succession of broad notched downward waves in the ventricular complex, in form suggesting defective conduction in the right

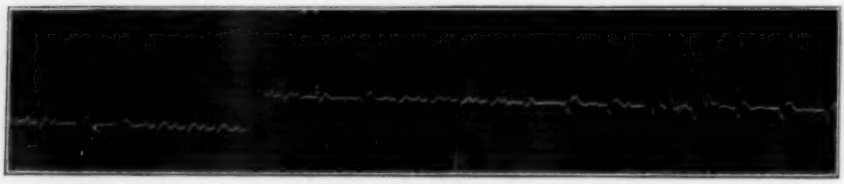

Fig. 15, Case 2.—Leads I and II, Nov. 23, 1914, 3 p. m.

branch of the bundle of His. After a brief interval another record of Lead 2 showed an admixture of ventricular complexes similar to those just described with complexes of normal supraventricular origin or with origin in the junctional tissue. Apparently complete dissociation had been maintained. In Lead 3 most of the ventricular complexes were of normal contour but there were occasional ones in which most of the complex was made up of a rather large downward deflection instead of the usual upward deflection. These downward deflections were not blunt or notched. Twenty minutes later complete dissociation apparently had persisted with now a larger number of ectopic beats in all three leads (Figs. 13 and 14), giving a considerable variation in the type of succeeding complexes.

At 3 p. m. on November 23 the curve in Lead 1 (Fig. 15) was very similar to that which was obtained at 9:25 a. m. on the same day, but the rate was slightly

more rapid. In Leads 2 (Fig. 15) and 3 (Fig. 16) there were considerably more ectopic ventricular beats of apparently various points of origin, and at places these occurred in rapid succession so as to suggest in places temporary ventricular fibrillation.

On the next day, November 24, at 11 a. m., at 3:45 and at 3:50 p. m. the rate was regular and the complex similar to those during the early stay in the hospital, while at 4 p. m. it had become irregular with one or two ectopic beats following the normal beat, consequently a bigeminal or trigeminal (Fig. 17) rhythm.

On November 25 and 26 no electrocardiograms were taken but the heart action judging by the pulse as felt appeared to be normal. On November 27

Fig. 16, Case 2.—Lead III, Nov. 23, 1914, 3 p. m.

Fig. 17, Case 2.—Lead III, Nov. 23, 1914, 4 p. m.

a normal curve was obtained. No others were taken between this time and the death of the patient on November 29 but in this period no pulse irregularity was noted.

CASE 3.—In this case the patient was in the Peter Bent Brigham Hospital (Medical No. 2043) from Dec. 15, 1914, to March 9, 1915, on which day death occurred. This patient was a woman, aged 58, who about Christmas time,

Fig. 18, Case 3.—Lead I, March 5, 1915.

1913, had a rather severe attack of indigestion and shortness of breath. She appears to have had similar symptoms for some time prior to this but never to such a marked degree. At this time dyspnea was severe enough to cause her to remain sitting up in a chair throughout the night. Under treatment she

improved so that she was in good condition until the middle of September, 1914, when the symptoms of Christmas, 1913, reappeared and in addition her legs swelled. These symptoms gradually increased and she became much weaker and feebler and lost considerable weight. When she came to the hospital her area of cardiac dulness extended 3 cm. to the right of the midsternal line and 16 cm. to the left. The heart rate was occasionally interrupted by extra systoles. No murmurs were heard. Her systolic blood pressure was 250. There was marked edema of the legs, abdomen and the lower back. Her eyes showed the picture of albuminuric retinitis. She had the urine of a chronic interstitial

Fig. 19, Case 3.—Lead II, March 5, 1915.

nephritis and functional tests showed that this was of an advanced degree. She gradually grew worse and died on March 9. Clinically it had been a case of chronic interstitial nephritis, hypertension, heart hypertrophy and chronic myocarditis. No necropsy could be obtained.

Electrocardiographic study on Dec. 16, 1914, showed the ventricular contour of a marked degree of left ventricular hypertrophy with a moderate number of ectopic beats of both auricular and ventricular origin. Electrocardiograms

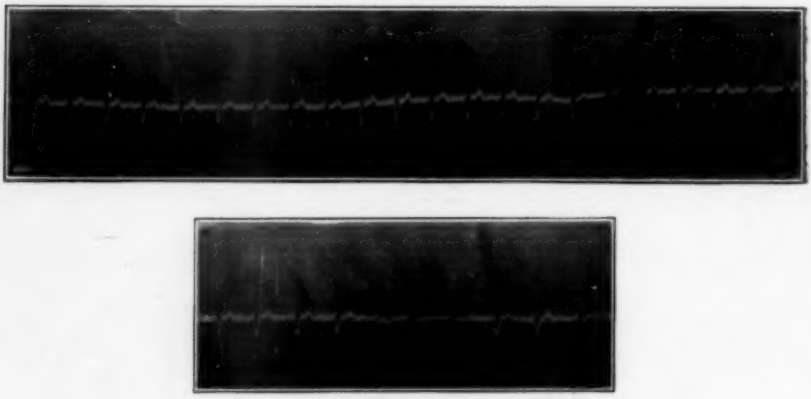

Fig. 20, Case 3.—Lead III, March 5, 1915.

on December 18 showed only ectopic auricular beats. Other electrocardiograms showed no ectopic beats. On March 1, 1915, electrocardiograms showed a typical picture of auricular fibrillation with no ectopic beats. On March 5, 1915, electrocardiograms showed at times a variety of ventricular complexes (Figs. 18, 19 and 20), often changing in contour from beat to beat. In this curve no definite "P" waves could be made out though in places there were suggestions of "P" waves. The ventricular rate was regular as compared with the curve of March 1 when there was definite auricular fibrillation. Con-

sequently it cannot be said definitely what was taking place in the auricles. It may be that there was auricular fibrillation with a regular idiopathic ventricular rate or it may be that the auricles were beating and auriculoventricular dissociation was present, but the curves did not give distinct evidence of this.

During the early part of the patient's stay in the hospital she had had from time to time small amounts of digitalis. From January 29 to March 2, no digitalis was given. On March 2, 8 c.c. of an infusion of digitalis was begun at 10 a. m. and continued three times a day until 7 p. m. on March 5 when it was omitted owing to the character of the electrocardiographic record obtained on that day. The general condition of the patient was growing much worse during and prior to this period of digitalis therapy. Only one electrocardiographic record was taken after March 5. It showed auricular fibrillation without ectopic beats. This was taken on March 8 slightly less than twenty-four hours before the death of the patient.

CASE 4.—In this case (Medical No. 2361) the patient was in the Peter Bent Brigham Hospital from Feb. 18, 1915, to March 18, 1915, on which day he was discharged. This patient, a man aged 68, about a year before admission began to notice that he was short of breath. Gradually this grew worse and he developed a cough with tenacious sputum. A distressed feeling in the region of his stomach with failing appetite and constipation ensued. No edema of his legs, however, developed. When he came into the hospital the area of cardiac dulness extended 3 cm. to the right and 14 cm. to the left of the midsternal line. A soft systolic murmur was heard at the apex and the heart sounds were fairly strong. The rate was moderately irregular of the extra systole type of arrhythmia as judged by the finger. The systolic blood pressure was 165 and the radial arteries showed pronounced sclerosis. In the bases of the lungs there were many coarse râles. The liver was slightly enlarged. No subcutaneous edema was made out. The case was regarded as one of chronic myocarditis and chronic nephritis. The patient improved in the hospital and was discharged in good condition. He received 5 c.c. of an infusion of digitalis three times a day from February 24 to February 27.

Electrocardiograms on February 18, 20, 23 and 24 showed a moderate number of ectopic beats of both auricular and ventricular origin and the ventricular complex of left ventricular hypertrophy. Pulsus alternans was present. On February 26, having started on digitalis on February 24 as previously described, the electrocardiograms showed the varying type of ventricular complex which has been described in the previous cases. However, the variations in type of ventricular complex were far less marked than in the cases previously described. The relation of auricular to ventricular beat could not be made out very satisfactorily as the "P" waves were indistinct. However, in places the "P" wave came very close to or was partially incorporated in the "R" wave so that it seems reasonable to suppose that the relation of the contraction of the auricle to the ventricle was similar to that in the previously described cases. On the next day there were found slight variations in some of the succeeding ventricular complexes. Subsequently on March 1, 5, 10, 12 and 13 the electrocardiograms were similar to those of the first days in the hospital.

Cohn offers three possible explanations for the varying ventricular complexes met with in his case. The first assumes a single permanent site in the main stem of the conduction system, above its division into right and left branches, as a source of stimulus to production and that this site is supposed to discharge impulses at regular intervals. Under this assumption the impulses are conducted now in one branch of the system and now in the other, the varying ventricular complexes depending on which branch the impulse traverses. The passage of the

impulse over one branch would, according to this interpretation, be the result of a temporary functional disturbance in the other. It assumes that complete dissociation between the contraction of the auricle and ventricle may be present as a temporary derangement, probably toxic, in the conduction system. The derangement must be of such a nature that impulses could not be conducted from auricles to ventricles, but could be conducted along that portion of the system in continuity with the ventricles, that is to say the portion between the A-V node and the distribution to the ventricular muscle.

The second explanation assumes that the site from which the impulses to contraction come is not fixed, but wanders from one side of the heart, that is to say of the conduction system, to the other. Cohn thinks that impulses so widely scattered as would have to be assumed here may give rise to an orderly succession of contractions, but that such an occurrence is unlikely.

The third explanation assumes that the stimuli to contraction arise synchronously or almost synchronously in the auricle and in the wall of the left ventricle, but the existence of block in Cohn's patient makes this unlikely. On the whole Cohn favors an intoxication as the basic cause of the phenomenon of varying ventricular complexes, assuming that his patient had digitalis intoxication.

Oppenheimer and Williams suggest in their case that the divergent types of ventricular complexes arise from the fact that the intrinsic ventricular pace-maker was frequently shifting or that the different impulses started at the same point and traveled either along different routes or at varying rates along the same route. As they found no anatomic lesion in the auriculoventricular system in their case they say that the heart-block may possibly be of neurogenic or circulatory origin or may be ascribed to chemical agents, to asphyxia or to some hindrance of the passage of impulses from terminal arborizations of the conduction system to the ventricular musculature.

In the cases which I have described variation in form of ventricular complexes was present similar to that described in the cases of Cohn and Oppenheimer and Williams, though not so marked in degree. In addition in my first case there was pairing of beats, a well-recognized digitalis phenomenon. My first patient had received digitalis from March 11 to March 15 in doses of 0.1 gram of powdered leaves every four hours and again from March 30 to April 4 in doses of 0.1 gram of powdered leaves four times a day. The first electrocardiograms taken on this patient were taken on March 20, five days after digitalis was stopped. These and those taken the following day showed the changing ventricular complexes. Subsequently normal cardiac rhythm was restored. On April 3, however, under digitalis therapy the phe-

nomena which occurred on March 20 and 21 reappeared. At necropsy the heart showed no evident lesion of the conduction system, and during life the blocking had been transitory. In my second, third and fourth cases the patients developed these changes under digitalis therapy and the condition was again transient. So it would seem that in my cases as well as in the others the variations in form of ventricular complexes were the result of digitalis action in individuals with hearts decompensated from myocardial insufficiency. Auriculoventricular dissociation developed as a result of digitalis and there was a further disturbance in conduction or in myocardial irritability leading to changing ventricular complexes. It is interesting in this connection that in my second case with auriculoventricular dissociation there appeared temporarily to be defective conduction in the right branch of the bundle of His in addition to the block higher up.

SUMMARY

As an occasional result of digitalis there develops a cardiac disturbance consisting of variations in the form of succeeding ventricular complexes. Of the cases, one reported by Cohn, one by Oppenheimer and Williams and four by myself, all except possibly one of my cases showed auriculoventricular dissociation.[8] In one of my cases the curve obtained did not justify any statement as to auricular activity; there may have been a regular rate in the auricles with auriculoventricular dissociation. All cases were of the type of chronic myocarditis without any marked signs of valve lesions.

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# THE INACTIVATION OF PEPSIN BY SODIUM CHLORID: ITS CLINICAL SIGNIFICANCE *

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The problem of the etiology of ulcer of the stomach has recently been approached from the point of view of that older problem—the nondigestibility of the stomach by its own digestive juice. For instance, Frentzel,[1] in 1891, and Katzenstein,[2] in 1908, showed that living stomach and duodenum implanted in the stomach were not influenced in any way, while small intestine and spleen under similar conditions were promptly digested. Katzenstein believed that the resistance of the stomach and duodenum to peptic digestion was due to the presence in the stomach wall of a specific inhibiting body—antipepsin.

In a more recent contribution, Katzenstein,[3] by reducing the antipepsin content of the stomach and blood (by methods not altogether clear), succeeded in producing chronic experimental ulcers in dogs' stomachs. He concluded that gastric ulcer is a sequence to a local injury of the stomach wall, whereby the normal balance between gastric juice pepsin, and gastric wall antipepsin, is disturbed.

While these conceptions are interesting and original, considerable doubt has arisen as to the validity and nature of this so-called antipepsin. Carl Oppenheimer, in his "Die Fermente und ihre Wirkungen," [4] after a critical survey of all available evidence, concludes:

> Im Allgemeinen ist es wohl wahrscheinlich dass hier keine echten Antikörper im Sinne der Immunitätslehre vorliegen. Es sind eher negative Katalysatoren.

He points out that this antipepsin is thermostabile, that it does not completely inhibit pepsin action, and that similar "antipepsins" may be found in extracts of yeast, molds and bacteria.

During the progress of research[5] on so-called antipepsin of the blood serum in 1911, I was able to show, in association with Dr. Jobling, that blood serum is capable of permanently binding pepsin and preventing it from digesting protein. We concluded from a con-

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* Submitted for publication May 2, 1915.

* From the Morris Institute for Medical Research and the Michael Reese Hospital, Chicago.

1. Frentzel (quoted by Kathe): Berl. klin. Wchnschr., 1908, xlv, 2136.
2. Katzenstein: Berl. klin. Wchnschr., 1908, xlv, 1749.
3. Katzenstein: Arch. f. klin. Chirurg., 1913, ci, 1.
4. Oppenheimer, C.: "Die Fermente und ihre Wirkungen," Ed. 3, Leipzig, 1910.
5. Hamburger: Jour. Exper. Med., 1911, xiv, 535.

siderable series of biochemical experiments that this inactivation of pepsin was not due to a specific antibody of the blood serum, but was due to a quantitative *nonspecific* pepsin deviation, similar to the deviation described for other ferments, notably trypsin.

In the development of a suitable technic for this work, a most interesting fact was observed, notably, that under certain conditions, sodium chlorid, used as physiological salt solution, would completely prevent pepsin from digesting protein. The conditions under which this inhibition occurred are simply that the ferment be made up in aqueous solution, with all trace of hydrochloric acid removed. If a faint trace of acid be present, or be added before sodium chlorid solution, no inhibition occurs. Moreover, hydrochloric acid added

TABLE 1.—INHIBITION OF PEPSIN BY SODIUM CHLORID

| Tube * | 0.85 Pct. NaCl c.c. | Water c.c. | N/10 HCl c.c. | 10 Minutes | 60 Minutes | 18 Hours | 24 Hours |
|---|---|---|---|---|---|---|---|
| 1 | 2.5 | ... | 0.5 | 0 | 0 | 0 | 0 |
| 2 | 2.5 | ... | 1.0 | 0 | 0 | 0 | 0 |
| 3 | 2.5 | ... | 5.0 | 0 | Trace? | 0 | 0 |
| 4 | ... | 2.5 | 0.5 | 0 | + | + + + | + + + + |
| 5 | ... | 2.5 | 1.0 | 0 | + | + + + | + + + + |
| 6 | ... | 2.5 | 5.0 | 0 | + | + + + + | + + + + |
| 7 | ... | ... | 0.5 | 0 | + | + + + | + + + + |
| 8 | ... | ... | 5.0 | 0 | + | + + + + | + + + + |
| 9 | ... | ... | 1.0 | 0 | + | + + + + | + + + + |

* In each tube was placed carmin fibrin and 0.0001 gm. pepsin in 1 c.c. water. All tubes were incubated for thirty minutes.

Sodium chlorid (2.5 c.c. of 0.85 per cent. solution) prevents pepsin in solution in water from digesting carmin fibrin; the addition of N/10 hydrochloric acid in excess does not reactivate ferment. Control tubes alone and with water show complete digestion in twenty-four hours. 0 = no digestion; +, + +, + + +, partial digestion; + + + + = complete digestion.

after sodium chlorid inhibition fails to reactivate the pepsin, the inhibition remaining permanent—*inactivation.* (Tables 1 and 2 will make these relations clear.) Under such conditions, sodium chlorid would likewise be considered an antipepsin.

It was our belief that this inactivation of pepsin (when in aqueous solution) by normal serum and by sodium chlorid were important factors in the action of so-called antipepsin, and that such inactivation was responsible for most, if not all, of the published accounts of antipepsin.

The inhibiting action of sodium chlorid on pepsin has been studied particularly by Schütz[6] and Levites.[7] In a physicochemical study of

6. Schütz: Beitr. z. chem. Physiol. u. Path., 1904, v, 406.
7. Levites: Ztschr. f. physiol. Chem., xlviii, 187.

the inhibiting effects of various salts on peptic digestion, Schütz arranged a table of their anions and cations in a decreasing order of their inhibiting action.

Levites, using other methods, came to practically similar conclusions, finding that the acid portion of the salt causes most active inhibition, that the metal portion was relatively slight, and that the salts of weak acids were more strongly inhibitory than those of strong acids.

We found, further, that if pepsin was dissolved in an acid solution strong enough to prevent inactivation by sodium chlorid, simple neutralization of this acidity alone (without addition of sodium chlorid) sufficed to cause inactivation. This is caused by the sodium chlorid formed from interaction of acid and alkali acting in a neutral

TABLE 2.—Protection of Pepsin by Hydrochloric Acid against Inactivation

| Tube * | Pepsin in 1 c.c. $H_2O$ gm. | Pepsin in 1 c.c. N/10 HCl gm. | N/10 HCl c.c. | 10 Minutes | 30 Minutes | 18 Hours | 36 Hours |
|---|---|---|---|---|---|---|---|
| 1 | 0.0001 | ..... | 0.5 | 0 | 0 | 0 | 0 |
| 2 | 0.0001 | ..... | 1.0 | 0 | 0 | 0 | 0 |
| 3 | 0.0001 | ..... | 5.0 | 0 | 0 | 0 | 0 |
| 4 | ..... | 0.0001 | 0.5 | + | + | + + + | + + + + |
| 5 | ..... | 0.0001 | 1.0 | + | + | + + + + | + + + + |
| 6 | ..... | 0.0001 | 5.0 | + | + | + + + + | + + + + |

* In each tube was placed carmin fibrin and 2.5 c.c. 0.85 per cent. sodium chlorid. All tubes were incubated for thirty minutes.

Sodium chlorid (2.5 c.c. in 0.85 per cent. solution) prevents pepsin in solution in water from digesting carmin fibrin, in spite of the subsequent addition (in excess) of N/10 hydrochloric acid. Pepsin dissolved in N/10 hydrochloric acid is not prevented from acting by sodium chlorid.

solution to cause inactivation, the ferment having been placed in a neutral solution by this same interaction. This last fact—the inactivation of pepsin—by the neutralization of acid pepsin, forms the basis for this report, particularly the significance of this finding in the neutralization of gastric juice.

Gastric juice was obtained from Pawlow dogs and by aspiration of the human fasting stomach in seven cases:

Normal stomach.

Alcoholic gastritis.

Hyperacidity—two cases.

Ulcer.

Carcinoma—two cases.

Peptic digestion was estimated by nitrogen determinations of the noncoagulable proteid of inactivated beef serum, after the method described in the work on antipepsin.

The following cases will serve as illustrations:

CASE 1.—B. S., male medical ward. Clinical diagnosis, gastric ulcer. Aspiration of fasting stomach: 20 c.c. bile-stained fluid, free hydrochloric acid 6, total acid 20.

TABLE 3.—INACTIVATION OF PEPSIN BY NEUTRALIZATION OF GASTRIC JUICE FROM ULCER PATIENT

| Flask | Gastric Juice c.c. | Neutralized Gastric Juice | Neutralized and NaCl Added | N/10 HCl c.c. | Beef Serum c.c. | Kjeldahl |
|---|---|---|---|---|---|---|
| 1 | 0.5 | 0 | 0 | 5 | 5 | 34.0 |
| 2 | 0.5 | + | 0 | 5 | 5 | 3.5 |
| 3 | 0.5 | + | + | 5 | 5 | 2.8 |

In Flask 1, the unchanged juice gave a digestion figure of 34 (Kjeldahl), while Flask 2, in which juice had been neutralized with tenth-normal sodium hydroxid, no digestion occurs (3.5 Kjeldahl resulting from control normal serum). In each flask the later addition of 5 c.c. hydrochloric acid fails to reactivate pepsin. In other words, the ferment is *permanently* inactivated (deviated), and prevented from causing further digestion by the simple neutralization of the gastric juice.

CASE 2.—I. S. Male medical ward. Clinical diagnosis, carcinoma. Aspiration of fasting stomach: 12 c.c. viscid yellow-green fluid; free hydrochloric acid, 0; total acid, 40.

TABLE 4.—INACTIVATION OF PEPSIN BY NEUTRALIZATION OF GASTRIC JUICE IN CARCINOMA OF THE STOMACH

| Flask | Gastric Juice c.c. | Neutralized Juice | Neutralized and NaCl Added | NaCl | N/10 HCl c.c. | Beef Serum c.c. | Kjeldahl |
|---|---|---|---|---|---|---|---|
| 1 | 0.5 | 0 | 0 | 0 | 5 | 5 | 18.8 |
| 2 | 0.5 | + | 0 | 0 | 5 | 5 | 3.0 |
| 3 | 0.5 | + | + | 0 | 5 | 5 | 4.6 |
| 4 | 0.5 | 0 | 0 | + | 5 | 5 | 17.7 |

This case is similar to the preceding, showing in addition in Flask 4 the inability of sodium chlorid alone to deviate ferment.

Although seven cases constitute a minimum number on which to draw conclusions, still the findings were so uniformly positive and so completely in accord with the earlier work, that it seemed unnecessary to gather a larger series. They showed constantly that the neutralization of gastric juice results in complete inhibition of peptic action *even after the addition of hydrochloric acid in excess,* and that the inhibition of pepsin is due to *sodium chlorid acting in a neutral medium.*

What is the mechanism of the inhibition of pepsin by sodium chlorid? While there is no direct experimental answer to this question, the explanation, I believe, rests on the modern conception of ferment action, as described by Michaelis,[8] Loeb,[9] and others.

Michaelis, with the aid of electrical conductivity readings, found that the proteolytic action of pepsin depends on its electrolytic dissociation, and that only the positively charged pepsin ions (cations) are capable of proteolytic digestion.

On the addition of hydrochloric acid to neutral pepsin, a salt is formed which may dissociate in one or both of two ways:

$$\text{Pepsin}_2 + HCl = [\text{pepsin}^+ + Cl^-]\ [H^+ + \text{pepsin}^-].$$

Of these only the cation pepsin (*pepsin*$^+$) is active. If, however, sodium chlorid be added in place of acid, a new salt is formed, sodium pepsin, which is proteolytically inactive because of the preponderance of inactive anions and absence of active cations:

$$\text{Pepsin}_2 + NaCl = [Na^+ + \text{pepsin}^-]\ [\text{pepsin}^+ + Cl^-].$$

Has this phenomenon of pepsin inactivation any clinical application? If so, its significance would lie in the ability to adopt measures whereby the stomach acid could be completely neutralized and the neutral reaction continuously maintained, and also that the newly formed and secreted acid could be immediately and continuously bound with alkali, as soon as it was formed. If this could be accomplished, the pepsin set free by neutralization, as well as the newly secreted pepsin, would be bound by inhibiting sodium chlorid and permanently inactivated and deviated. As a result, peptic activity would be destroyed for a period of time equal to the continuance of the neutral reaction, a condition similar to achylia gastrica. In fact, the findings would be those of a temporary achylia, with neutral or alkaline reacting stomach contents and total absence of peptic digestion.

Under what conditions would such a temporary achylia be desirable? First, as a prophylactic measure, to prevent the formation of gastric or duodenal ulcer. Second to facilitate the healing of ulcer by removing the factor which, next to mechanical trauma, is probably of greatest importance in the continuance and progression of chronic ulcer. Therefore, in simple hyperacidity, in hypersecretion from whatever cause, in motor insufficiency with continuous secretion, in pylorospasm with hyperacidity and hypersecretion, in chronic ulcer, in gastroenterostomy to prevent the formation of jejunal ulcer, neutralization with peptic inactivation might be desired.

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8. Michaelis and Davidsohn: Bioch. Ztschr., 1911, xxxvi, 280.
9. Loeb: Bioch. Ztschr., 1909, xix, 534.

The present methods of treatment of these hyperacid conditions with alkaline substances, attempt to control or lessen the chemical discomfort and to *reduce* the degree of acidity—particularly of the free hydrochloric acid. While such methods are of highest importance, it is evident, from these experiments, that the ideal of alkaline treatment is not merely the lessening of gastric acidity, but, of probably far greater importance, *the complete and continuous neutralization of the acid contents of the stomach*—to the end that pepsin be deviated and peptic digestion prevented.

The endeavor to demonstrate and maintain complete, continuous neutralization of the gastric contents is being made at the present time. By means of a Rehfuss stomach tube, kept constantly in the stomach for days at a time, fractional aspirations and readings of the stomach contents can be made at any time, and the degree of acidity or alkalinity measured. By this means, the effect of various foods, methods and time of feeding, neutralizing strength of various alkaline substances, can be directly measured and recorded. The results from these investigations are too few to warrant publication at this time. In general, however, it may be said that by the use and combination of certain of these alkaline substances, combined with certain foods and methods of feeding, continuous, complete neutralization of the stomach contents can be demonstrated and maintained.

## CONCLUSIONS

1. Sodium chlorid will prevent pepsin in aqueous solution from digesting protein. This confirms the work of Schütz and Levites on the inhibiting action of various salts on peptic digestion.

2. The inhibition of pepsin by sodium chlorid, together with the ability of animal serum to deviate pepsin (described in an earlier paper), is responsible for most, if not all, of the published accounts of antipepsin.

3. The inhibition of pepsin by sodium chlorid is permanent, the inactivated ferment failing of reactivation by the subsequent addition of hydrochloric acid. The inactivation may be prevented, however, by dissolving the ferment in dilute hydrochloric acid.

4. Neutralization of pepsin dissolved in hydrochloric acid alone (without the addition of sodium chlorid) inhibits the ferment by the sodium chlorid formed from union of alkali and acid, acting in a neutral solution. Complete neutralization of the gastric juice causes similar pepsin inactivation.

5. The inactivation of pepsin by complete and continuous neutralization of gastric juice is indicated in the treatment of various diseases

of the stomach in which temporary inhibition of peptic digestion is desired. This is particularly true in the prevention and cure of chronic gastric ulcer. By the use of certain foods, methods and time of feeding, and various alkaline substances, complete and continuous neutralization can be obtained.

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# ENDEMIC TYPHUS FEVER IN THE PHILIPPINE ISLANDS

## OBSERVATIONS BASED ON A STUDY OF TWENTY-THREE CASES OCCURRING AMONG FILIPINOS AT CAMP KEITHLEY, MINDANAO, P. I., WITH THE RESULTS OF ANIMAL INOCULATIONS *

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Endemic typhus fever has not been reported, heretofore, as occurring in the Philippine Islands. Reference to the Reports of the Director of Health,[1] from July 1, 1911, to Jan. 1, 1914, shows that occasional cases resembling typhus fever have occurred in Manila, but "not sufficient confirmatory evidence could be obtained as to the correctness of the diagnosis to warrant reporting them as typhus."

It is believed that sufficient data—clinical, laboratory and epidemiologic—are embodied in this report to show that typhus in endemic form unquestionably exists in the Philippines, at least in the Lanao section of Mindanao.

Twenty-three cases have been studied in the military hospital at Camp Keithley. The first case, erroneously diagnosed as malaria, was admitted Aug. 28, 1914. During September four additional cases were under observation, and it became evident that the disease was not one of those ordinarily encountered.

Tentative clinical diagnoses of typhus fever were made in these cases by elimination; but, in the absence of confirmatory laboratory evidence, the first positive diagnosis was not made until October 12.

The disease observed here corresponds to the acute infectious disease described by Brill[2] of New York which, subsequently, was proved by Anderson and Goldberger[3] to be identical with the typhus fever of Mexico. In our cases the period of incubation appeared longer, the average leukocyte count was less and marked nervous manifestations—absent in Brill's cases—were not uncommon in ours.

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* Submitted for publication March 19, 1915.

1. Ann. Rep. Bureau Health, Philippine Islands, Dec. 31, 1912, p. 94; ibid., June 30, 1913, p. 131; ibid., Dec. 31, 1913, p. 102.

2. Brill, Nathan, E.: An Acute Infectious Disease of Unknown Origin; a Clinical Study Based on 221 Cases, Am. Jour. Med. Sc., April, 1910, p. 484.

3. Anderson, John F., and Goldberger, Joseph: The Relation of So-Called Brill's Disease to Typhus. An Experimental Demonstration of Their Identity, Pub. Health Rep., Feb. 2, 1912.

Although in general our cases fall into the category of Brill's disease, an occasional case was encountered which approximated in severity the epidemic typhus of Europe. One case in particular was strikingly like a case of European typhus in an immigrant which I had the opportunity of observing clinically, and subsequently at necropsy at the Philadelphia Hospital for Contagious Diseases in 1906.

The disease does not coincide with the descriptions of the Manchurian typhus observed during the Russo-Japanese War, and the temperature curve, with its steep rise during invasion and abrupt decline, differs from the more gradual curve described as occurring in the typhus fever of Mexico.

The following general description fits the average case observed during this endemic. Variations from the usual picture were common and these will be considered as special features of the disease.

### SYMPTOMS

The period of incubation in those cases in which it could be arrived at with any degree of certainty varied from ten to fourteen days. Prodromes were absent. The onset was abrupt, a chill ushering in the disease in twenty-one of our twenty-three cases. Headache, usually frontal, followed the initial chill quite constantly and invariably constituted the dominant symptom. In six cases vomiting occurred at the onset, and 25 per cent. of those observed complained of backache and pain in the extremities. Fever immediately followed the onset. The temperature rose rapidly to 103 or 104 F. and, reaching its fastigium on the second or third day, remained elevated, with morning remissions and evening exacerbations, for about a week. Defervescence, occurring in the usual case about the tenth day, was by crisis or rapid lysis through forty-eight hours. The pulse was full and bounding, relatively slow as compared to the fever and was not dicrotic.

The patient was seen within forty-eight hours after the onset as a rule. He was apathetic, and looked dull and stupid, but was not mentally confused. The face and neck were flushed or turgid, the temporal veins engorged and prominent and the conjunctivae injected. The bowels were either constipated or regular, there being no tendency to diarrhea. The lips were usually parched, sometimes fissured, and sordes on the lips and teeth was constantly noted in the severer cases. The tongue resembled that of typhoid fever, being coated along the dorsum and clean at the tip and edges. Early in the disease the tongue was swollen, moist and flabby, becoming dry and covered with a heavy brown coating later. The breath had a heavy musty odor not unlike that of typhoid fever. Nervous manifestations in the form of tremor of the hands, tongue and lips were present from the beginning.

Tremulous speech was less constant but not infrequent. Prostration and profound anorexia developed early.

About the third day the spleen could be palpated. On the fourth day subcuticular mottling, most marked in the dependent parts, was noted. The eruption was observed on about the fifth day, beginning on the abdomen and chest and rapidly spreading to the extremities. The so-called tache cérébrale—the appearance of a red line on the skin when stroked with the finger—was demonstrated constantly. It appeared early and could be elicited for several days after the eruption had disappeared. The headache and other subjective signs usually ameliorated on about the sixth day, and the patient became comparatively comfortable.

The crisis could be looked for on about the tenth day. Preceding the crisis the patient became restless and nervous and the brow was usually moist. Profuse sweating and diuresis were almost invariably concomitants of the crisis, while diarrhea and vomiting occurred occasionally. Following the crisis all symptoms ameliorated, the spleen receded and the eruption faded rapidly. More or less prostration was usual for twenty-four hours after the crisis, following which the tongue cleaned, the appetite returned and convalescence was established with a rapidity that was striking and all out of proportion to the clinical picture preceding it.

SPECIAL FEATURES

The *onset* was characterized by chill in twenty-one cases, headache in nineteen and by vomiting in six. Lumbar pain and pains in the extremities occurred in eight cases and vertigo was recorded once. In two of the cases the onset was gradual and fever was the first symptom noted. There was intense pain in the chest in one case at the onset, probably due to pulmonary congestion.

The *facies* at the onset was that of intense congestion—face flushed, temporal veins prominent and conjunctivae injected. The expression in some cases was anxious and in others dull and stupid. The color remained good until the crisis, after which pallor was evident for a variable time and the patient exhibited a "washed out" appearance.

The *temperature* rose rapidly during the stage of invasion, reaching the fastigium on the second to the sixth day. The average fastigium in twenty-one cases was 103.5 F., the lowest 102 F. and the highest 104.6 F. The fastigium was reached on the third or fourth day in 50 per cent. of the cases. In about two-thirds of the cases an initial drop or remission of from 3 to 5 degrees occurred on the second, third or fourth day. This single early remission occurred with sufficient fre-

quency to constitute a special feature of the temperature curve; and that it occurs, apparently, in typical cases of typhus fever, witness the temperature charts from Murchison,[4] Wilson[5] and Doty.[6]

After reaching the fastigium the usual curve was that of continued fever, with morning remissions of a degree or two, until defervescence. The fever was distinctly remittent in five of our twenty-three cases, remissions of over 2 F. occurring daily in these cases. An occasional case was encountered in which the fever was irregular and conformed to neither the continued nor remittent type. Defervescence was by crisis in fourteen cases, by rapid lysis in six, and in the remaining three cases the type was too doubtful to classify. A pseudocrisis followed by recurrence of fever occurred seven times. Pseudocrises were noted from the fifth to the twelfth days. Crises occurred from the fourth or fifth day, in mild or abortive cases, to the twelfth or fourteenth day in the severer cases. Lysis covered a period varying from forty-eight to ninety-six hours. The febrile period in this series of cases ranged from six to sixteen days, terminating from the tenth to the fourteenth day in the majority. The temperature was considered normal when the evening temperature reached 98.4 F. After defervescence the temperature usually oscillated for three or four days, remaining within a degree of normal, and then became subnormal for a period varying from two or three days to a week. Slight chills and chilly sensations, during the course of the disease, occurred in two cases.

The *skin* of the face, neck, upper part of the chest and of the back and shoulders was suffused during the early days of the disease. Sweating was unusual before the crisis, being noted but twice. Sudamina did not occur. Herpes labialis was observed in one case. The so-called tache cérébrale was a constant phenomenon. It could be elicited before the eruption appeared and after its disappearance. In eleven of the twenty-three cases the skin became mottled on the fourth or fifth day and the characteristic eruption followed.

The *eruption* occurred in sixteen cases, was absent in two cases and in the remaining five cases, which occurred during the first part of the endemic, the rash was either absent or overlooked. It appeared on the fifth day in two-thirds of the cases, but in isolated cases it was observed as early as the fourth day and as late as the eighth day. It appeared first on the abdomen and chest and, developing rapidly

4. Murchison, in Osler: Principles and Practice of Medicine, Ed. 8, New York, D. Appleton & Co., 1912, p. 354.

5. Wilson: Medical Diagnosis, Philadelphia, J. B. Lippincott Company, 1909, p. 642.

6. Musser: Medical Diagnosis, Ed. 5, Philadelphia, Lea Brothers & Co., 1904, p. 703.

and not in crops, had extended to the back, shoulders, arms, hands, legs and feet and in two cases to the face within twenty-four hours. The lesions were discrete, slightly raised, rose-red to dark red, irregular in outline and measured from 2 to 8 mm. in diameter. Some of the spots were hyperemic and disappeared on pressure; others darker red, were modified but not entirely blanched by pressure, while an occasional spot here and there was distinctly petechial, fading gradually after the eruption had disappeared and leaving dirty yellowish stains in the skin. In individual cases the lesions numbered from a few dozen to many hundreds. In the average case the spots were much more profuse than the rose-spots of typhoid and less numerous than the lesions in the average case of measles. The eruption faded rapidly with the crisis and had disappeared by the tenth day. Desquamation did not occur.

The *blood* showed certain constant changes. The leukocyte count, in sixteen cases, varied from 4,000 to 18,000, the average count being 7,865. Differential leukocyte counts showed a rather consistent increase in the percentage of large mononuclear cells, with a corresponding decrease in the number of polymorphonuclears. Eosinophils were not present in appreciable numbers during the febrile period. These observations are in accord with those of Wilson[7] at Belfast, who states that a relative increase in the large mononuclears, especially toward convalescence, was very characteristic and that during the febrile period eosinophils were absent or scanty.

The average differential count in sixteen cases showed polymorphonuclears 55 per cent., lymphocytes 25 per cent., large mononuclears 16 per cent., eosinophils 0.8 per cent. and basophils 0.2 per cent. Unfortunately, routine estimations of hemoglobin and red cell counts were not made. Clinically, however, there appeared to be anemia of varying degree following defervescence of the fever. In considering the blood changes, the fact should be mentioned that feces examination showed that the majority of the patients harbored intestinal parasites.

*Blood cultures* in fifteen cases gave negative results. Blood was taken from a vein, and flasks of plain broth or dextrose broth were inoculated at the bedside. Both aerobic and anaerobic cultures remained sterile after from three to ten days incubation at 37 C. In justice to the contention of Plotz,[8] who recently reports having isolated an anaerobic organism from cases of typhus fever in New York, I confess that the technic employed in making anaerobic cul-

7. Wilson, W. J.: The Etiology of Typhus Fever, Jour. Hyg., August, 1910, quoted by Balfour and Archibald; Second Review, Wellcome Research Laboratories, Khartoum, 1911, p. 387.

8. Plotz, Harry: The Etiology of Typhus Fever and of Brill's Disease, Preliminary Communication, Jour. Am. Med. Assn., 1914, lxii, 1556.

tures here was, of necessity, crude. Tubes of dextrose-broth were heated to drive off as much oxygen as possible, cooled rapidly, inoculated, and the surface of the medium was covered with a layer of sterile oil to exclude oxygen. Obviously, the degree of anaerobiosis obtained by this method was only relative, but more approved methods could not be resorted to with the facilities at hand.

The *pulse* exhibited no characteristic features. Early in the disease it was of good volume and tension, relatively slow as compared to the temperature, and dicrotism was absent. A pulse rate over 100, with the temperature ranging between 102 and 104 F., was the exception rather than the rule. The critical fall in temperature was occasionally

TABULATED RESULTS OF LEUKOCYTE COUNTS

| Case No. | Day of Disease | Leukocytes | Polymorphonuclear Per Cent. | Lymphocytes Per Cent. | Large Mononuclears Per Cent. | Eosinophils Per Cent. | Basophils Per Cent. |
|---|---|---|---|---|---|---|---|
| 1 | 4th | 11,500 | | | | | |
| 1 | 7th | 18,000 | 72 | 12 | 15 | 1 | |
| 8 | 7th | 5,000 | 61 | 20 | 18 | 0 | 1 |
| 9 | 3d | 6,600 | 68 | 23 | 15 | 1 | |
| 10 | 3d | 8,400 | 77 | 12 | 11 | | |
| 11 | 2d | 8,000 | 50 | 23 | 25 | | |
| 12 | 3d | 5,000 | 25 | 25 | 50 | | |
| 13 | 2d | 10,000 | 45 | 39 | 15 | 1 | |
| 14 | 2d | 5,000 | 57 | 30 | 12 | | |
| 15 | 5th | 4,000 | 65 | 25 | 9 | .. | 1 |
| 16 | 4th | 6,000 | 65 | 19 | 15 | 1 | |
| 17 | 6th | 8,600 | 67 | 23 | 11 | | |
| 18 | 5th | 6,800 | 58 | 32 | 16 | | |
| 19 | 3d | 7,500 | 55 | 35 | 10 | | |
| 20 | 9th | 6,000 | 57 | 29 | 11 | 3 | |
| 21 | 5th | 8,500 | 63 | 29 | 7 | 1 | |
| 22 | 3d | 8,200 | 51 | 24 | 19 | 6 | |

accompanied by a rise in the pulse rate to 120 or 130; but considered throughout the disease the pulse was a slow one like that of typhoid fever.

The *heart* showed no variations from the normal except in one case. A soft blowing systolic murmur was audible in this case following the crisis. The point of greatest intensity shifted and the quality of the murmur changed from day to day, and these peculiarities, in conjunction with the temperature curve of sepsis, led to a clinical diagnosis of acute endocarditis, which was confirmed subsequently at necropsy.

*Digestive System.*—Anorexia developed early and persisted throughout the febrile period. It was profound in 30 per cent. of the cases. The tongue was flabby, moist and swollen early in the disease, coated along the dorsum and clean at the tip and edges. Later

the tongue became dry and the coating darker and thicker. In the severer cases the lips were parched and fissured and sordes collected on the teeth. Nausea and vomiting occurred at the onset in six cases and during the course of the disease in four cases. In one case it was so persistent that the patient could retain nothing but champagne. Intestinal symptoms were conspicuous by their absence. Meteorism, abdominal pain, tenderness or diarrhea were not encountered once in twenty-three cases. The spleen could be palpated below the costal margin in twelve of the twenty-three cases. The enlargement occurred early, being elicited on the second or third day in six cases, on the fourth day in three, while in the remaining three cases it was demonstrable on the fifth, sixth and seventh days, respectively. The liver was palpable in but one case. Scleral jaundice was observed once.

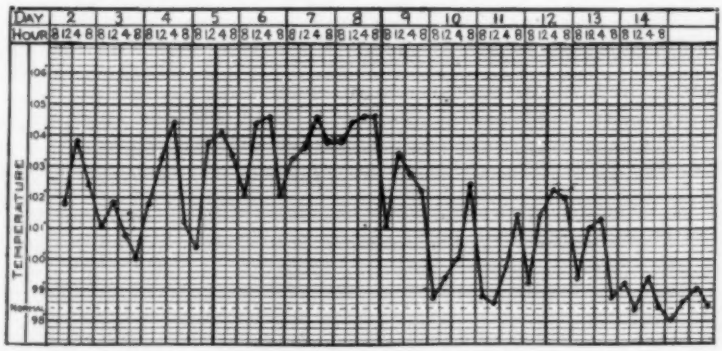



Chart 1.—Temperature chart in a severe case of typhus.

*Respiratory System.*—Epistaxis, so constant a feature in typhoid fever, occurred but twice in our series; once on the second day while the patient's face was almost purple from congestion, and in the second case on the ninth day, preceding the crisis. Irritative cough without physical signs to account for it was observed twice. Hypostatic congestion and edema of the lungs occurred as terminal features in one case. Pleurisy with effusion complicated one case.

*Nervous System.*—Signs referable to the nervous system were common, and it appeared to stand the brunt of the infection. Constant harrassing headache constituted the dominant symptom to the patient's mind. It developed at the onset and usually persisted until the sixth day. It was frontal as a rule, but in some cases the head ached "all over" and in one case the pain was occipital. Tremor of the tongue was observed in nineteen cases, of the lips in fifteen cases, of the hands in fourteen, and six of the patients had tremulous speech. The trem-

ors were course and of the intention variety, becoming apparent on voluntary efforts such as protruding the tongue, talking, or buttoning the pajama shirt. In two cases tremor of the tongue was incoordinate in character, and the patients instinctively held the organ protruded with the aid of the teeth. Delirium occurred in two cases. It was low and muttering without noisy manifestations in both instances and in both cases it preceded the crisis. Coma vigil, carphologia, subsultus tendinum and relaxation of the sphincters occurred in one case. Visual hallucinations were recorded once. Insomnia, ascribable to the constant harassing headache, occurred in 26 per cent. of our cases. Tinnitus aurium and partial deafness in both ears, transitory in character, followed the crisis in one case.

*Urinary System.*—Retention of urine occurred rather persistently in one case, necessitating frequent catheterization. Polyuria was an almost invariable concomitant of the crisis. The urine was high colored and showed the usual febrile changes—concentration, high specific gravity, marked acidity and increase of solids. Albumin, sugar or casts were not demonstrated. The kidneys showed moderate parenchymatous degeneration at necropsy in one case.

*Relapse.*—A relapse, intercurrent in character, occurred in one case. During the initial febrile movement the temperature became subnormal on the morning of the sixth day, and then oscillated between 97 or 98 and 100 F. until the fifteenth day, the evening temperature never reaching normal. From the ninth to the fifteenth day the patient was up and about and desired to return to duty. On the sixteenth day he had a distinct chill, and the temperature suddenly rose from 97.2 to 102 F. Blood was negative for malaria, and careful physical examination failed to reveal any cause for the chill and fever. The fever of the relapse continued for twelve days. Constipation, backache, profound anorexia and nervousness accompanied the relapse. No eruption was observed.

### MORTALITY

One death, due to acute ulcerative endocarditis following the crisis, occurred in the series of twenty-three cases, establishing a death rate of 4.34 per cent.

### DIAGNOSIS

Sporadic cases of the disease observed here would have undoubtedly been diagnosed as cases of fever of undetermined type, as the teaching has been that typhus fever is a disease of cold or temperate climates, and one would think of the possibility of its existence in the Philippines only after having thoroughly eliminated every other possibility. Having established the identity of the primary cases, the diagnosis of subsequent cases was not difficult.

Clinically, the striking features of the disease were intense headache, conjunctival injection, tremor of tongue, hands and lips, and the history of an initial chill followed by an abrupt rise of temperature. An eruption appearing usually on the fifth day, in conjunction with the foregoing features, clinched the diagnosis. The so-called tache cérébrale was a constant feature and, although it may be elicited occasionally in other diseases, its constancy was an aid to diagnosis in our cases. Negative findings of importance were the absence of plasmodia in the blood and the failure to cultivate any organism from the blood by ordinary methods. A history of living in, or having visited, an endemic center was also of value.

Isolated cases of this disease might be confounded with measles, relapsing fever, cerebrospinal meningitis, uremia, pneumonia, or in the

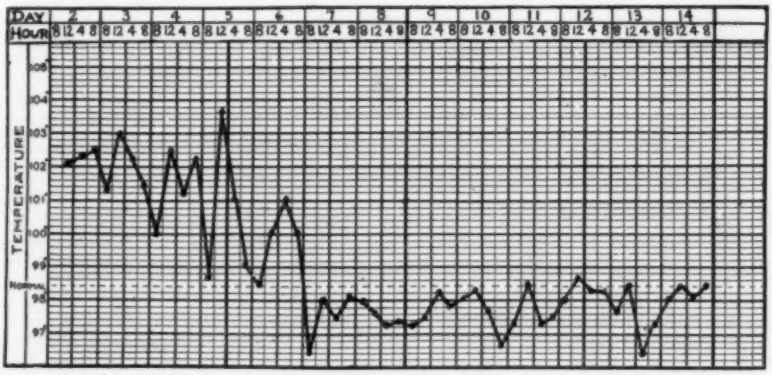



Chart 2.—Temperature chart in a mild case of typhus.

preeruptive stage, with smallpox. In reviewing the endemic, however, these diseases may be dismissed at a glance. The disease bore certain resemblances to other diseases which require more careful differentiation, and these will be considered seriatim.

*Typhoid fever* is characterized by a gradual onset, the course of the fever is longer, defervescence is by lysis and convalescence is not rapid. Abdominal symptoms, absent in our cases, constitute a prominent feature of typhoid. The eruption of typhoid appears on the seventh or eighth day and consists of rose-colored spots. In our cases the eruption could be looked for on the fifth day, and the spots were darker in color and more profuse than those of typhoid. The typhoid bacillus may be isolated from blood cultures in 90 per cent. of typhoid cases during the first week of the disease, while, in our experience, blood cultures were uniformly negative. An additional factor is that

our patients, with the exception of five civilians, had been immunized against typhoid by protective inoculation, and, although an occasional case of typhoid may be expected among those who have been immunized, the possibility of numerous cases occurring is extremely remote.

*Dengue,* as remarked by Manson, "bursts upon a place" and the majority of those in the community are stricken with certainty and rapidity following the introduction of the first case. The disease is characterized by a two-phased fever, marked arthritic and muscular pains, constant leukopenia and a tendency to slow convalescence during which rheumatic stiffness and twinges in the muscles and joints are common. In contrast to this picture, our cases showed no tendency toward pandemicity, the temperature curve was that of continued fever, pains in the muscles and joints were not harassing, the leukocyte counts frequently showed slight or moderate leukocytosis, and convalescence was rapid and uninterrupted.

*Influenza,* another pandemic disease, may be dismissed because of the endemic character of our cases and the absence of catarrhal symptoms.

*Malaria* may be eliminated in view of the uniform absence of plasmodia in the blood of our cases, the character of the temperature curve, and the negative results of therapeutic tests with quinin.

### EXPERIMENTAL TYPHUS IN ANIMALS

Three monkeys and ten guinea-pigs were inoculated with blood from various cases of the series—mild and severe—during the febrile period.

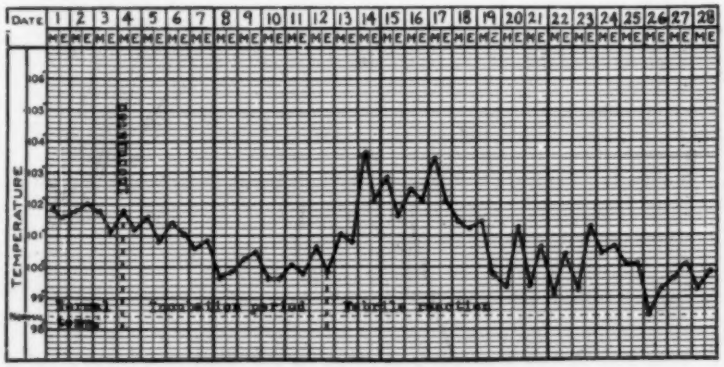
The blood was drawn directly from the median basilic, or median cephalic vein and, without being defibrinated, diluted with saline solution or otherwise treated, was injected intraperitoneally at the bedside. The amount of blood injected was uniformly 3 c.c., and the intraperitoneal route was the one invariably chosen.

Brief protocols of the experiments follow:

MONKEY 1 (Mike).—Male; nativity, Samar, P. I.; species undetermined but one that is common in the Philippines; weight, 5½ pounds. Inoculated intraperitoneally with 3 c.c., of blood from Case 14. The patient was in the third day of the disease at the time the blood was taken and was extremely ill. The eruption was just appearing. The monkey was in robust health. His normal temperature, taken morning and evening for three days prior to inoculation, ranged between 101 and 102.2 F. Following inoculation there was a gradual daily fall in temperature for six days; but the animal was responsive, appetite was normal and there was no evidence of illness until the tenth day. In other words, the incubatory period of nine days was silent. On the tenth day following inoculation, the animal sat huddled up, his fur was ruffled, and, in contrast to his previous behavior, he lay perfectly quiet while the temperature was taken. As the attendant expressed it, he was "droopy." The tem-

perature began to rise, reaching its fastigium — 103.4 F. — seven days after the onset of illness. On the following day, the eighth day of illness, the temperature dropped 4 degrees by crisis. The animal was weak and unresponsive for several days following the crisis, and emaciation, which became evident at that time, persisted for several weeks. No eruption was noted.

MONKEY 2 (Pat).—Male; nativity, Samar, P. I.; same species as Monkey 1; weight 9½ pounds. Inoculated intraperitoneally with 3 c.c. of blood from Patient 15, at the time in the fifth day of his illness, with eruption out all over the body and symptoms marked. The course of the disease in this animal was essentially the same as in Monkey 1. The period of incubation was approximately eight days, during which the animal remained well. During the febrile period of seven days signs of illness — huddled posture, ruffled fur, anorexia and lassitude — were evident. The temperature reached its fastigium — 103.6 F. — within thirty-six hours of the onset, remained elevated four days and declined by rapid lysis, the entire febrile period occupying about seven days. The normal temperature of this animal lay between 101 and 102 F. during the three days preceding inoculation. Emaciation became evident after the fever declined. No eruption was detected.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TEMPERATURE
106
105
104
103
102
101
100
99
98
Normal temperature
Normal temperature
Incubation period
Febrile reaction

Chart 3.—Febrile reaction in Monkey 2, following intraperitoneal inoculation with blood from a typhus case.

MONKEY 3 (Moro).—Male; nativity, Mindanao, P. I.; species common in Mindanao, but different from that of Monkeys 1 and 2; weight 6 pounds. Inoculated intraperitoneally with 3 c.c. of blood from Case 17 on the seventh day of illness. Patient was not severely ill. In this animal no palpable evidences of illness were detected. During the second week following inoculation there was questionable fever, but the reaction was too doubtful to classify as positive.

GUINEA-PIG 1.—Inoculated intraperitoneally with 3 c.c. of blood from Case 8. Blood taken on the seventh day while the disease was at its height. Reaction doubtful.

GUINEA-PIG 2.—Inoculated in same manner as previous animals with blood from Case 9, the one case of the series which terminated in death. Reaction questionable.

GUINEA-PIG 3.—Inoculated in the usual manner with blood taken from Case 10, one of the mildest clinically of the series. Blood taken on the sixth day of the disease. In this animal there was a well-marked incubatory period of ten days during which the animal showed nothing abnormal. On the eleventh

day the temperature began to rise, reaching 103.6 F. on the seventeenth day. During the night the temperature dropped sharply to 100 F., and the animal lay huddled in a corner, obviously ill. Respirations were rapid and shallow and the animal refused to eat. The temperature again rose sharply to 103.8 F. and then declined, the animal dying the following afternoon, eighteen days after inoculation and about eight days after the onset of illness. Necropsy showed congestion and edema of the lungs. No other gross changes were demonstrated.

GUINEA-PIG 4.—Inoculated in the routine manner from Case 11 during the third day of the disease. Temperature rose sharply to 104 F. in twenty-four hours. It declined gradually to 101 F. and, running a continuous course between 101 and 102 F. for two weeks, suddenly dropped to 99 F., the point at which it had registered when the animal was inoculated. In the absence of a definite incubation period in this case, the reaction was classified as doubtful.

GUINEA-PIG 5.—This animal received intraperitoneally 3 c.c. of blood from Case 12, taken on the fourth day of the disease. The temperature curve was readily divided into three parts — incubation, febrile period and postfebrile period — at a glance. The period of incubation was ten days. The fever reached its fastigium on the second day following the onset, ran a continuous course for seven days, and defervescence occurred by rapid lysis in thirty-six hours. The febrile period occupied approximately ten days.

GUINEA-PIG 6.—Inoculated in the usual manner with blood from Case 13. Blood taken on the fourth day. Except for an abrupt rise in temperature to 103 F. on the sixth day following inoculation, which may have heralded an abortive attack, nothing significant was noted, and the result was classified as questionable.

GUINEA-PIG 7.—Inoculated from Case 14, together with Monkey 1, during the third day of the disease. Result negative.

GUINEA-PIG 8.—Received intraperitoneally 3 c.c. of blood from Case 15 during the fifth day of the disease. The temperature of this animal had been taken morning and evening for five days preceding inoculation, and the incubation period and febrile movement that followed were clearly defined. The period of incubation occupied nine days, and the fever, abrupt in onset and ending by crisis, lasted five days.

GUINEA-PIG 9.—This animal was inoculated intraperitoneally with 3 c.c. of blood from Case 16. Blood taken on the fifth (?) day of the disease. Temperature ranged between 99 and 101.4 F., and this being within the limits of normal in the guinea-pig, it was believed that the result was negative. On the twenty-sixth day after inoculation, however, the animal died. Necropsy showed the entire thoracic cavity filled with fluid blood and recent clots. The pericardium was intact and contained no blood. The right lung was atelectatic and the lymph nodes at the root of the lung were enormously enlarged, pale, and breaking down. Source of intrathoracic hemorrhage, although searched for diligently, could not be found. Hemorrhage probably occurred from erosion of a pulmonary vessel embedded in the mass of glands at the root of the lung. The liver and kidneys showed slight parenchymatous degeneration. Smears from the lymph nodes stained with Wright's stain, and by approved methods for the demonstration of tubercle bacilli, were negative for bacteria. Cultures remained sterile for ten days.

GUINEA-PIG 10.—Received intraperitoneally 3 c.c. of blood taken from Case 17 on the seventh day of the disease. The animal died suddenly ten days after inoculation. On opening the chest at necropsy the pericardium was distended with blood, on removal of which rupture of the right ventricular wall was revealed. The myocardium showed moderate parenchymatous change. There was intense pulmonary congestion.

Summarizing the results of the experimental inoculations recorded above, it will be noted that a definite febrile reaction occurred in 53.8 per cent. of the inoculated animals, while in the remaining 46.2 per cent. the reaction was negative or too questionable to be classified.

The incubation period varied from eight to ten days, during which the animal remained well. This was followed by an abrupt or gradual rise of temperature, the fastigium being reached on the second to the seventh day. The febrile period occupied from five to ten days, and the temperature defervesced by crisis or rapid lysis through forty-eight hours. In addition to fever, two monkeys and one guinea-pig exhibited loss of appetite, ruffling of the hair, huddled posture and "droopiness." An eruption was not observed. Emaciation was evident in two monkeys for a considerable time after recovery. Death terminated the infection in three instances.

In comparing these results with those of others, notably Nicolle and Conseil,[9] Anderson and Goldberger,[10] and Ricketts and Wilder,[11] it is believed that our attempts to infect monkeys and guinea-pigs with the virus of endemic typhus fever were successful.

Anderson and Goldberger[10] outline the typhus reaction observed in monkeys as follows:

> Following an inoculation with virulent material the monkey continues for a period varying from five to twenty-four days as if nothing had happened. . . . In about 90 per cent. of the cases the incubation period varies between six and ten days.
>
> At the end of this period the temperature of the susceptible animal rises fairly rapidly as a rule, sometimes gradually or at times very abruptly. The fever reaches its fastigium in thirty-six to forty-eight or seventy-two hours; it then continues for a variable period of one or two to five or more days, then defervesces. The defervescence, like the invasion, is variable; although usually gradual, it is frequently rapid or even critical. In brief, the course of the fever in the monkey is essentially like that of the fever in man.
>
> The fever may be accompanied by loss of appetite, thirst, a ruffling of the hair, and a drooping posture; very commonly, however, even with a well-defined febrile reaction, the animal except for some slight listlessness shows hardly any outward manifestations. In other words, the fever is the only definite index of a reaction. . . . In about 76 per cent. of the cases the fever varies in duration between six and ten days.
>
> At the termination of the fever there is almost always manifest some degree of emaciation.

They state, further, that in their experience a very large proportion —22.5 per cent.—of monkeys possess at least a transitory immunity to

9. Nicolle and Conseil: Ann. de l'Inst. Pasteur, April and May, 1912; abstr., Progr. Med., March, 1913, p. 225.

10. Anderson and Goldberger: Natural and Induced Immunity to Typhus Fever, Tr. Fifteenth Internat. Cong. Hyg. and Demography, ii, Part 1, p. 17.

11. Ricketts and Wilder: The Transmission of the Typhus Fever of Mexico (Tabardillo) by Means of the Louse (Pediculus Vestamenti), Jour. Am. Med. Assn., 1910, lv, 1304.

the injection of virulent typhus blood from infected monkeys, and that inoculation of virulent blood from man, whether New York or Mexico City cases, was successful in only a few cases. This explains the apparently negative result following inoculation in our Monkey 3 (Moro).

In 1912, Nicolle and Conseil[9] demonstrated that the guinea-pig is susceptible to infection with typhus when inoculated intraperitoneally with from 2 to 4 c.c. of blood from man or monkeys. The incubatory period varied from seven to sixteen days. This was followed by fever lasting from four to eleven days, with an average of about a week. Toward the end of the febrile period there was a small loss in weight. They conclude that unless the temperature be taken, the infection may pass unobserved; in other words, the temperature curve is the only index of infection.

Results similar to these have since been reported by Anderson[12] and by workers[13] in the Research Laboratories of the New York Department of Health.

## EPIDEMIOLOGY

*Climate.*—Camp Keithley is on the north shore of Lake Lanao, Mindanao, P. I. It is 8 degrees north of the equator. Reference to the Medical History of the Post shows that the annual rainfall during the year July 1, 1908, to June 30, 1909, was 98.46 inches. The highest monthly rainfall was 22.14 inches and the lowest 3.22 inches. There is practically no dry season. According to the geographic definition, the post is in the heart of the tropical zone; but owing to the altitude and the proximity of a large body of water fed by cold mountain streams, the climate is temperate rather than tropical. Palms, the presence of which constitutes "the truest expression of the tropical clime," do not flourish. The heat is never sufficient to cause one the slightest discomfort while, on the other hand, blankets at night are not only desirable but necessary for comfort.

Typhus fever is preeminently a disease of cold and temperate climates. As Castellani and Chalmers[14] point out, the disease appears in the tropics at high altitudes, principally, and it quickly dies out with the onset of hot weather. We are told that the typhus of Mexico (tabardillo) occurs constantly on the great Mexican plateau, while in the coast towns the disease is rarely encountered.

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12. Anderson, John F.: The Problem of Typhus in the United States, Jour. Am. Med. Assn., 1913, lx, 1846.

13. Nicoll, Krumweide, and others: Collected Studies, Bureau of Laboratories, N. Y. Dept. of Health, 1912-1913, vii, 132.

14. Castellani and Chalmers: Manual of Tropical Medicine, Ed. 2, New York, William Wood & Co., 1913, p. 1094.

In view of the recently acquired knowledge that the disease is transmitted by the louse, it is difficult to connect its occurrence in the tropics with the peculiar climatic conditions incident to altitude. The louse is omnipresent—in the lowlands as well as in the hills. The explanation may lie in the fact that the coast natives, unaccustomed to the chilly night air of the highlands, hermetically seal their quarters and huddle together for greater warmth, thus not only creating filth, overcrowding and bad ventilation—predisposing factors which lower their resistance to infection—but, by more intimate contact, augmenting the passage of the transmitting agent from one to the other.

*Season.*—The twenty-three cases studied during the present endemic were evenly distributed, practically, over the months of September, October and November, the latter part, roughly, of the so-called rainy season.

*Sex.*—Males constituted 82.62 per cent. of the patients, while 17.38 per cent. were females.

*Age.*—Practically all the cases occurred in the third decade of life. Not a single case was seen in a child, and this is remarkable because of the large number of children exposed in the endemic foci from which the majority of the cases came. It is in harmony, however, with the experiences of Nicolle and Conseil[15] at Tunis. They found that nursing infants are immune to infection, and that older children may have the disease in so mild a form that it may escape detection. This emphasizes the importance of recognizing mild cases of typhus in children which, unrecognized, may act as missing epidemiologic links and cause the continuance of an outbreak.

*Endemic Foci.*—Two distinct foci from which the disease disseminated were detected in connection with this endemic. The primary focus was a corral that had been converted into living quarters for families of enlisted men of the twenty-fifth and twenty-eighth companies, Philippine Scouts. The building is 170 feet long and 36 feet wide and is divided into twenty-six stalls, 14 feet deep by 10 feet wide, with two small rooms at each end. The building was converted into living quarters by closing in the stalls with sheets of iron roofing and building floors of scrap lumber. No provisions for lighting or ventilation existed, and the quarters were damp, dark and poorly ventilated. Twenty-seven compartments in this building were occupied by 103 persons—thirty men, thirty-one women and forty-two children—living in filth and squalor. Superficial examination showed the heads of many of these people infected with pediculi. That many of the

15. Nicolle and Conseil: Gaz. d. hôp., April 9, 1911, p. 609; abstr. Progr. Med., March 1913, p. 228.

women and children were ill-nourished needs no emphasis when it is remembered that they were dependent for their subsistence on native soldiers whose monthly wage is $7.50.

Filth, overcrowding, poor ventilation, ill nourishment and vermin combined to form exact conditions for the spread of typhus fever.

Two of the occupants gave a clear-cut history of recent attacks of fever, which undoubtedly was typhus in view of the information subsequently received from a typhus patient infected by these people. Three other women looked ill, and one of these may have been convalescing from typhus, as her husband was subsequently under observation with well-marked symptoms.

The second endemic focus was the so-called barrio of Bungalow just beyond the limits of the military reservation and under the jurisdiction of the civil authorities of Dansalan. This barrio is composed of native shacks, tenanted by scout soldiers and their families.

The first three cases encountered were in married men who, when not on duty, slept at the corral. The fourth case was in a recruit who had not been away from the reservation and as he gave a history of having visited the corral, and other possibilities were not elicited, the assumption was that infection had been contracted on one of these visits. The fifth, sixth and seventh cases were, like the first three, in married men who lived at the corral. The information elicited from the eighth patient, an officer's servant, stamped the corral as the undoubted source of infection. She stated that she frequently visited the wife of a corporal of the Twenty-Eighth Company, who lived at the corral, and that she invariably visited there on Saturdays and Sundays. September 21 and 22 she slept at the corral and stated that the corporal's wife was ill with calentura (fever) at that time; that the woman was taken ill, September 8, and that her illness lasted two weeks. The corporal, who nursed his wife, was taken ill September 22, and was ill ten days. The officer's servant became ill October 5, fourteen days after sleeping at the corral.

Patients 10, 11 and 14 lived at the corral and were infected there unquestionably. The source of infection in Cases 13 and 15 was not ascertained with certainty. They had visited the corral eleven and twenty-four days prior to the onset of illness, respectively, and although an incubation period of twenty-four days is unusual, it is possible that both were infected at that time. Patient 16 had a family quarantined at the corral, and it is possible that he—as occurred in two other instances—had broken quarantine and was infected during a clandestine visit.

Patient 18 was admitted to the hospital on the fifth day of the disease. She lived at Bungalow and was the first case from that endemic

focus. She had formerly lived at the corral but denied having visited there for several months. Patient 19 was a recruit who probably contracted the disease while visiting a brother living in the house in Bungalow from which Case 18 was taken. Patient 23, the brother whom Patient 19 had visited, was admitted subsequently. Patients 20 and 21 were both married men who lived at Bungalow, and it seems reasonable to connect them with the other cases of infection there.

The source of infection in Cases 12, 17 and 22 could not be ascertained.

*Origin of the Endemic.*—Efforts to trace this endemic to a single original case have been unsuccessful. The clinical records of the last thousand cases admitted to the hospital at Camp Keithley have been reviewed, and from them six cases of fever have been culled which resemble cases of typhus observed during this endemic. The first of these cases was admitted May 28, 1913, another occurred in June, a third in July, and two more in December. The sixth case was admitted in February, 1914. Diagnoses of malaria were made in four of the cases, one was diagnosed intestinal autointoxication, and the sixth was diagnosed as paratyphoid fever. The malarias exhibited courses of fever similar to that of typhus, plasmodia were not demonstrated and quinin in large doses did not influence the temperature curve. The clinical records show no other instances of paratyphoid infection, and, as the diagnosis of paratyphoid fever in the sixth case was made in the absence of confirmatory evidence from the laboratory, it is believed that it should be viewed with considerable mental reservation. The diagnosis "intestinal autointoxication" is very frequently open to suspicion.

If we accept these instances of probable cases of typhus fever, the history of the disease extends back to May, 1913, at least.

My predecessor, Captain Pipes, of the Medical Corps, informed me that he had encountered cases of fever in Moros identical with the first case of typhus observed here, and was very anxious that the identity of the disease, the nature of which had not been determined at that time, be established. Information from various sources is in accord with Captain Pipes' statement. Mr. Moore, at the time acting provincial fiscal, recently related the occurrence of a fever similar to ours among the Cotabato Moros, and Captain Fletcher, P. S., states that the Moros of Romain Valley, in this province (Lanao), who live in old overcrowded cottas, report many cases of a fever that is attended with high mortality.

It is probable that typhus has existed in endemic form in Mindanao for an indefinite period, being looked on by the native, as all fevers are, as a form of malaria.

Whether the disease was originally introduced by religious pilgrims returning from Mecca, where typhus occurs in epidemic form, or whether it may have followed the lines of commercial intercourse from Japan are matters of conjecture.

*Transmission.*—Experimental transmission of the disease to monkeys by means of the louse, along the lines pursued by Anderson and Goldberger,[16] Ricketts and Wilder,[11] and others was not attempted. In the absence of proper facilities for safeguarding such experiments, there would have been constant danger of infected lice escaping, and the attempts would have been foolhardy.

The epidemiologic data point, however, to the louse as the probable transmitting agent, and the evidence is strengthened by the fact that preventive measures aimed at ridding patients and contacts of lice broke up two proved endemic centers, and resulted in the disappearance of the disease.

A striking characteristic of this endemic, in connection with the theory of louse transmission, which is in accord with the experiences of those who have followed epidemics of typhus in Tunis, Belfast and Mexico City, is that the disease has been connected invariably with squalid environment. Our cases did not come from the families of officers, from the quarters of American noncommissioned officers, or from company barracks, although these places are not immune to the visitations of measles, malaria or dengue when such diseases are prevalent. On the other hand, the disease occurred constantly among those having more or less intimate daily contact with native women. The explanation may be that the louse occurs in the former places only under most exceptional circumstances, while it is as indigenous to the native woman as the flea is to the dog.

Entomologists state that the body louse (*Pediculus vestamenti*) is not found in the Philippines.[17] This is interesting, as it is the louse that is commonly believed to be the transmitting agent in typhus fever. However, Anderson and Goldberger[16] have recently demonstrated that the head louse (*Pediculus capitis*) is also capable of transmitting the disease, and the fact that the body louse is not found here does not weaken my conviction that the louse was the means of transmission during the recent endemic.

Flying insects, such as the mosquito or fly, may safely be ruled out as possible transmitting agents, as the disease remained restricted to

16. Anderson and Goldberger: The Transmission of Typhus Fever, with Especial Reference to Transmission by the Head-Louse (Pediculus Capitis), Pub. Health Rep., March 1, 1912.

17. Insects and Disease, Health Bull. No. 11, Bureau of Health, P. I., 1913, p. 15. Ann. Rep. Bureau of Health, P. I., June 30, 1912, p. 95.

areas beyond which it would have been carried with certainty by such intermediaries. No evidence was adduced that would inculpate the bedbug or flea. Transmission by food or drink is too remote a possibility to consider. That aerial transmission or fomites played no part in the dissemination of the disease seems evident in view of the fact that neither attendants nor other patients became infected at the hospital, where contact with fomites from typhus patients was more or less unavoidable for a period of three months.

I believe that consideration of the data outlined above justifies the opinion that the disease described is typhus fever. Further investigation along the line of experimental transmission by means of the louse would be interesting, and it is believed that the identity of this fever and Brill's disease might be established by cross-immunity tests with animals inoculated in the United States.

Anomalous fevers are common in the Philippines, and it is unfortunate that research workers confine their activities so largely to Manila, while interesting fields for investigation in the provinces are neglected. Field work similar to that prosecuted by officers of the Public Health Service in the southern United States would illuminate the medical geography of the Philippine Islands.

# SOME CONSIDERATIONS IN THE STUDY OF INFANTILE TETANY, WITH REPORT OF A CASE *

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For years it has been known that the effect of an inorganic salt on the irritability of nerve and muscle tissue is influenced by the presence of another salt in the solution. Ringer[1] was the first to discover that the twitchings of a frog's muscle produced by immersing it in an isotonic solution of pure sodium chlorid, were abolished by the addition of a small amount of calcium. J. Loeb[2] pointed out that the toxicity of a sodium chlorid solution was not due solely to the absence of calcium, but also to the presence of the sodium ion, since distilled water had no such toxic action. He also suggested that irritability depends on various ions, especially the metallic ions, Na, Ca, K and Mg, existing in definite proportion in the tissue.

But since the effect of an alteration in these proportions varies widely in different species of animals, no general law embracing the action of these ions has yet been formulated, and for particular tissues and species, the result of any salt disturbance must be determined.

In spite of this, clinical investigation in tetany has been largely directed towards a study of calcium metabolism, and the discussion of its pathogenesis has largely centered around the calcium content of the tissues. The clinical results, however, have not been satisfactory or in any way conclusive. The almost constant co-existence of rickets with infantile tetany has presented further difficulty in the interpretation of the results, and changes in the calcium balance may be secondary to the amount of calcium deposited in the bones and not due to any change in the content of the nerve substance or body tissues in general. In experimental tetany produced by parathyroidectomy, an increased loss of calcium occurs, and administration of calcium reduces, temporarily although never permanently, both the electrical irritability and the severity of the convulsions. Other salts, however, such as magnesium and strontium also produce this effect. Mac-

* Submitted for publication May 29, 1915.

* From the Department of Pathological Chemistry, University of Toronto, and the Sick Children's Hospital, Service of Dr. Alan Brown.

1. Ringer: Jour. Physiol., 1886, vii, 291.
2. Loeb, J.: Am. Jour. Physiol., 1910, iii, 383; Jour. Biol. Chem., 1905, i, 427.

Callum, Lambert, and Vogel[3] were able to produce extreme nerve hyperexcitability by perfusion of an organ with blood the calcium of which had been removed by dialysis.

Clinical results have been somewhat less constant. As a general rule, during the onset of the eclampsia, a decrease in the calcium retention occurs, and the reverse sets in during convalescence. The symptoms of the disease also can often be partially checked by the injection of a calcium salt. But this loss of calcium is not always found (Stoeltzner[4]) and administering calcium either with the food or by injection is frequently without result (Haskins and Gerstenberger[5]).

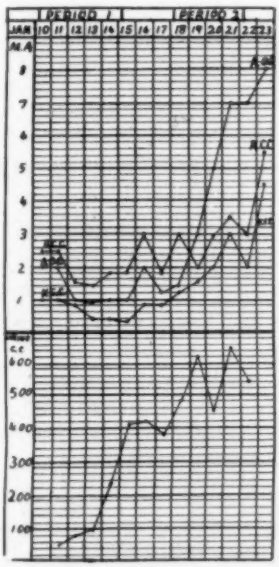


Chart showing variations in the electrical irritability and in the volume of the urine during periods of observation.

More recently, attention has been given to the effect of the other kations. It has long been the experience of pediatricians that cow's milk and particularly whey will aggravate infantile tetany; yet the organic constituents of milk (casein, fat, or sugar) have by themselves no such untoward effect. On the other hand, the inorganic salts of milk do affect the irritability, and this can frequently be demonstrated clinically. Calcium and magnesium, when administered

3. MacCallum, Lambert and Vogel: Jour. Exper. Med., 1914, xx, 149.
4. Stoeltzner: Jahrb. f. Kinderh., 1906, lxii, 661.
5. Haskins and Gerstenberger: Jour. Exper. Med., 1911, xiii, 314.

subcutaneously, bring about, as a rule, a temporary fall in the irritability and a quiescence of the tetany. This is especially the case with magnesium, which, following the recommendations of Behrend,[6] is frequently used with considerable success as a means of combating the convulsions. The salts of the alkalies act in the opposite direction. Grulee,[7] on adding sodium or potassium chlorid to the food of spasmophilic children, obtained an increase in the irritability. Lust[8] confirmed these observations and obtained most striking results with potassium. He also records a case of tetany in which each exacerbation was accompanied by a temporary increase of weight, due to a retention of salts and fluid, the so-called metabolism edema.

These facts suggest that the effect of inorganic salts on nervous tissue is not so much determined by the concentration of any one ion, but rather by their relationship to each other, and that it is some disturbance of the usual equilibrium that upsets the normal reaction of the nerve cell. A few years ago, Aschenheim[9] made estimations of the brain tissues in spasmophilia and found that, while the calcium and magnesium were most frequently decreased, sometimes they were unchanged and the sodium and potassium increased, the only constant factor being an increase in the quotient $\frac{Na + K}{Ca + Mg}$. He therefore concludes that the hyperexcitability is due to an increase in this factor. Further support of this hypothesis has been furnished by the researches of Reiss.[10]

Clinically very little work has been done to determine under what conditions these salt disturbances in tetany are induced and what the underlying factors are in their production. In recording the following case, a preliminary report of an investigation being carried on in Toronto along this line is presented.

### CASE REPORT

*History.*—G. McK., male, aged 13½ months, was admitted Jan. 7, 1915, to the Infants' Department at the Sick Children's Hospital. Breast fed for nine months, supplemented with Allenbury's food for part of time, and then with arrowroot biscuit. Diarrhea at 3 months of age, lasting one month. Lately fed on Horlick's malted milk. Dec. 15, 1914, the first attack of tetany occurred, lasting about half a minute; described as a stiffening of the body accompanied by the spasm of the hand and foot characteristic of tetany. Before this, he had been constipated for some time and, until time of admission, bowel movements were produced only by enemata, the stools being small and hard. December 24 a more severe and prolonged attack took place, during which the child

6. Behrend: Monatschr. f. Kinderh., 1913, xii, 269.
7. Grulee: Jour. Am. Med. Assn., 1912, lix, 938.
8. Lust: München. med. Wchnschr., 1913, lx, 1482.
9. Aschenheim: Monatschr. f. Kinderh., 1910, ix, 366.
10. Reiss: Ztschr. f. Kinderh., 1911, iii, 1.

became cyanosed and seemed to struggle for breath. Similar convulsions then occurred at frequent intervals. During this period he became cross and irritable and cried almost constantly.

*Examination.*—Examination on admission showed a child under weight for age, with a fair amount of subcutaneous tissue of diminished turgor. Feet and hands in typical position of carpopedal spasm. Spleen slightly enlarged. Slight craniotabes and enlargement of the epiphyses of long bones (evidence of rickets). Cried, while being examined, continuously, with occasional crowing inspiration. Chvostek's and Trousseau's symptoms present. Muscle jerks easily elicited. Odor of acetone in breath.

*Treatment.*—He was offered a milk mixture made up of evaporated milk, ounces 10, barley flour, ounces 1½; lactose, ounce 1, water, up to ounces 40. Eight ounces were given every four hours, five times a day. A good deal was at first refused. Cod liver oil (20 min.) and phosphorus (gr. 1/300) three times a day. Jan. 10, 1915, he was put in a metabolism bed and observed up to January 15. During this period of five days he was obstinately constipated, having three dark, yellow, foul-smelling stools produced in each case by half an ounce of castor oil. He became more restless and irritable. The laryngospasm increased. The electrical irritability on January 10 was: K. C. C. 1, A. O. C. 2, A. C. C. 2.5, and on January 15: K. C. C. 0.4, A. O. C. 1.0, A. C. C. 1.8. The weight increased from 13 pounds 9 ounces to 14 pounds 3 ounces, and, during this period, very little urine was passed, although the amount increased towards the end of the period. Signs unchanged, no convulsions.

January 16, 1 gm. of urea was added to the food daily to stimulate the diuresis which had already begun. From January 18 to January 22 observations were again made. During this period a striking change occurred. The child took more food and became less restless; the bowels moved without the use of castor oil, and the stools became lighter in color and less offensive. The urine flow was much freer; the electrical irritability decreased from K. C. C. 1.2, A. C. C. 3, A. O. C. 1.4 on January 18 to K. C. C. 2, A. C. C. 3, A. O. C. 7 on January 22. An increase of four ounces in weight occurred The carpopedal spasm disappeared. Trousseau's sign could not be obtained, and a slight twitch only could be seen in eliciting Chvostek's symptom.

Subsequently the child continued to improve and went on to good recovery.

During the periods of observation the patient was placed in a metabolism bed, the amount of food taken each day measured, and a proportionate part used for analysis. The urine and feces were collected separately. The specimens were dried and ashed by Bunge's method. Sodium and potassium were weighed as chlorids, and separated by platinic chlorid. The calcium and magnesium were weighed as calcium oxid and magnesium pyrophosphate, following McCrudden's[11] method. The electrical irritability was determined by placing the anode or kathode over the head of the fibula and the neutral pole over the abdomen. The minimum current which would produce a contraction of the peronei was estimated in milliamperes.

The case presented an opportunity for observation during a period of intensification of the symptoms and during a period of improvement. Variations in the electrical irritability and in the urine secretion are shown in the accompanying chart.

11. McCrudden: Jour. Biol. Chem., 1910, vii, 83.

The daily average estimations made of Period 1 are shown in Table 1.

TABLE 1.—Daily Average Metabolism Estimations in Period 1

| | Amount gm. or c.c. | Sodium Oxid | Potassium Oxid | Calcium Oxid | Magnesium Oxid |
|---|---|---|---|---|---|
| Milk..... | ..... | 0.1754 | 0.5460 | 0.4686 | 0.0324 |
| Feces..... | 14.6 | 0.0194 | 0.0387 | 0.0779 | 0.0076 |
| Urine..... | 176.0 | 0.0129 | 0.0609 | 0.0017 | 0.0216 |
| Total loss..... | ..... | 0.0323 | 0.0996 | 0.0796 | 0.0292 |
| Balance..... | ..... | +0.1431 | +0.4464 | +0.3890 | +0.0032 |
| Balance in per cent. of intake | ..... | 81.6 | 81.7 | 83.1 | 9.8 |

A marked retention of all the salts has occurred, which would go hand in hand with the retention of fluid and the gain in weight of this period. But this retention has not been uniform, and its outstanding irregularities are, first, the large amount of potassium (0.4464 $K_2O$); second, the small amount of magnesium (0.0032 MgO).

The relative proportion of alkali to alkali earth $\frac{Na + K}{Ca + Mg}$ is 1.501.

The results from Period 2 were as shown in Table 2.

TABLE 2.—Daily Average Metabolism Estimations in Period 2

| | Amount gm. or c.c. | Sodium Oxid | Potassium Oxid | Calcium Oxid | Magnesium Oxid |
|---|---|---|---|---|---|
| Milk..... | ..... | 0.2706 | 0.8331 | 0.6948 | 0.1136 |
| Feces..... | 51.7 | 0.0099 | 0.0770 | 0.2478 | 0.0279 |
| Urine..... | 585.0 | 0.1157 | 0.5359 | 0.0081 | 0.0149 |
| Total loss..... | ..... | 0.1256 | 0.6129 | 0.2559 | 0.0428 |
| Balance..... | ..... | +0.1450 | +0.2202 | +0.4389 | +0.0706 |
| Balance in per cent. of intake | ..... | 53.2 | 26.4 | 63.2 | 62.1 |

Here the proportions are reversed. The retained potassium has been cut in half, a daily balance of 0.4464 being reduced to 0.2202, and, while the former represents 81 per cent. of the intake, the latter is only 26.4 per cent. of the potassium in the food. The sodium retention has increased 0.002 gm., but the balance in terms of the intake has decreased from 81.6 per cent. to 53.2 per cent. The calcium balance has decreased from 83.1 per cent. to 63.2 per cent. of the intake, and its absolute value has increased 0.050 gm. only; but the balance is now nearly twice that of any of the other metals. The magnesium balance has increased almost twenty-fold, i. e., from 0.0032 to 0.0706, or, in

per cent. of the intake, 9.8 per cent. to 62.1. In the second period the quotient $\frac{Na + K}{Ca + Mg}$ is reduced to 0.717.

Examination of the calcium estimations by themselves would not lead one to believe that calcium changes could be held responsible for the development of tetany, and the figures demonstrate that actual loss of calcium is by no means essential for its production. In fact, the irritability has increased over a period of five days during which 0.3896 gm. of CaO were being daily retained in the tissues. Examined in connection with the other metals, the relative increase in the calcium retention during the second period becomes quite evident, being greater than the weight of the three other metals combined.

During this period of improvement, the body has been excreting the alkalies of the food and it is of special clinical interest to observe that nearly all of this excretion was performed by the kidney. This excretion occurred simultaneously with an increased flow of urine, whereas in the first period, during which the alkalies were retained, the kidneys were remarkably inactive. At the same time the restoration of the normal salt equilibrium took place along with an improvement in the gastro-intestinal system. The stools became less offensive and the bowels less constipated; the appetite improved and more food was taken. The association of fluid retention and gastro-intestinal disturbance, observed in the first period, is seen not infrequently in children, and the former seems to depend directly on the digestive disturbance since observation has shown that it can be controlled by dietetic changes, and disappears as the digestion improves. Carbohydrates and the salts of sodium and potassium are especially liable to induce these fluid changes and may well be reduced when there is any reason to believe that fluids are being retained. Taking away part of the whey from the food, as is sometimes done in the treatment of tetany, is a means of lowering the sodium and potassium intake; the calcium remains in the curd.

The importance of the kidney in regulating the salt equilibrium is evident from the figures given, and, when the urine is small in amount, the kidney may be stimulated by means of an organic diuretic—such as urea—1 gm. of which was given daily with the food.

The high magnesium balance is noteworthy in view of the specific action of magnesium upon nerve tissue. Its narcotic effect led Behrend[6] to use it in checking the symptoms of tetany. He found, however, that the magnesium, when given subcutaneously, is excreted again within twenty-four hours, and that injections must be repeated daily. A similar experience has been had in rickets, in which calcium, if injected, is not retained; yet, as convalescence begins, this loss stops and the tissues regain the power of retaining calcium. So in tetany,

with improvement, the body begins to re-establish the normal salt relationship, and the ability of the tissues to hold magnesium may be an evidence of a subsidence of the disease.

To sum up briefly: Clinical observation would not warrant the conclusion that calcium changes alone account for the nerve irritability in tetany, but would seem to support the hypothesis that the tetany results from a disturbance of the concentration equilibrium of the salts.

Such salt changes are probably associated with gastro-intestinal disturbances and decreased activity of the kidney, and, as improvement in the function of these two systems occurs, restoration of the normal salt equilibrium ensues. Treatment, accordingly, from these indications should aim at restoring a normal digestion and increasing the activity of the kidney.

# A SIMPLE METHOD FOR DETERMINING VARIATIONS IN THE HYDROGEN-ION CONCENTRATION OF THE BLOOD *

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AND
W. McKIM MARRIOTT, M.D.
BALTIMORE

Human blood, as it exists in the body, is faintly alkaline in reaction: that is, it has a hydrogen-ion concentration only slightly less than that of pure water, and this degree of alkalinity tends to be maintained even when considerable quantities of acid are produced within the body, or are introduced from without.

To a relative increase in the acid content of the body, the term "acidosis" is applied. Acidosis, conceivably, may be brought about in other ways than those just mentioned—for example, by decreased excretion of acid or by loss of bases from the body. The condition has been recognized in a variety of ways, such as increase in the ammonia coefficient of the urine, decrease of carbon dioxid tension in the alveolar air, the finding of abnormal acids in the blood and urine, by increased alkali tolerance and by diminished titratable alkalinity of the blood serum, by changes in the hemoglobin dissociation curve and by actual determination of the hydrogen-ion concentration of the blood. Production of ammonia, lowering of carbon dioxid tension in the alveolar air and in the blood, and excretion of acids are all part of the compensatory mechanism of the body, and it is only when this mechanism becomes overtaxed that appreciable changes in the hydrogen-ion concentration of the blood occur. The blood itself, owing chiefly to the "buffer" action of the carbonates of the plasma and phosphates of the corpuscles, can take up considerable amounts of acid or alkali without much change in its reaction. It is principally due to the work of L. J. Henderson[1] and his collaborators that we have a clear conception of the mode of action of these "buffers." An appreciable change in the hydrogen ion concentration of the blood indicates a failure of the protective mechanism and the presence of a significant acidosis. Herein lies the peculiar value of a determination of the hydrogen-ion concentration of the blood.

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* From the Pediatric and Medical Clinics, Johns Hopkins Hospital.

1. For a full discussion, see Henderson, L. J.: Ergebn. d. Physiol., 1909, viii, 298.

A brief word of explanation may be given for those unaccustomed to the physicochemical methods of expressing the reaction of a solution. A solution is acid when it contains an excess of hydrogen over hydroxyl ions, neutral when hydrogen and hydroxyl ions are in equal numbers, and alkaline when hydroxyl ions predominate. An acid of "normal" strength contains, in one liter, a gram of hydrogen capable of forming hydrogen ions,[2] and its strength may be expressed as 1 N. Diluting such a solution ten times, we would have 1/10 N or a solution containing 1/10 gram of actual or potential hydrogen ions to the liter. Continuing the process of dilution until 1/10,000,000 normal acid is obtained, we would have in such a solution 1/10,000,000 gram of hydrogen ions. Pure water, however, dissociates to form hydrogen and hydroxyl ions, and at 20 C. contains approximately 1/10,000,000 gram of hydrogen ions to the liter and an equivalent amount of hydroxyl ions (that is, 17 gm.). That is to say, pure water, our standard of neutrality, is 1/10,000,000 N acid and also 1/10,000,000 N alkaline. To avoid writing large figures it is customary to use the logarithmic notation and to express 1/10,000,000 N as $10^{-7}$N or, more conveniently, as suggested by Sörensen,[3] to drop the 10 and minus sign and say[4] pH7. If we have less than 1/10,000,000 gram of hydrogen ions to the liter, the solution is less acid than water, that is, it is alkaline — so, pH8 means actually 1/1,000,000 N alkali. The higher the exponent the more alkaline, or what is saying the same thing, the less acid is the solution.

To sum up:

pH1 = N/10 acid.

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pH6 = N/1,000,000 acid.
pH7 = *NEUTRALITY*.
pH8 = N/1,000,000 alkali.

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pH14 = N/10 alkali.

The reaction of the blood serum varies approximately between pH7 and pH8, the neutral point, pH7 being reached only in severe uncompensated acidosis, and a reaction of pH8 being attained perhaps only after administration of alkalies.

The measurement of the pH of the blood as compared with that of inorganic solutions presents many difficulties. The standard gas chain electrometric method has been applied to the blood by a number of investigators. A full review of the literature up to 1910 is to be found in an article by Botazzi.[5] More recent determinations have been made

2. For the sake of simplicity we will consider here only a "strong" acid and assume it to be completely ionized in dilute solution.

3. Sörensen: Ergebn. d. Physiol., 1912, xii, 401.

4. CH7 and $[H^+] = 7$ are synonymous expressions. Intermediate values, as, for example, between pH7 and pH8, are commonly expressed in one of two ways, as $0.25 \times 10^{-7}$ or pH = 7.6. The latter method is used in this paper. The conversion of one expression into the other is simple. For example, log. 0.25 = — 0.602, then $0.25 \times 10^{-7} = 10^{-0.602} \times 10^{-7.0} = 10^{-7.602}$ or pH = 7.602.

5. Botazzi: Der Harn sowie die übrigen Ausscheidungen und Körperflussigkeiten, edited by C. Neuberg, Berlin, 1911.

by Hasselbalch and Lundsgaard,[6] Peters,[7] Peabody[8] and Milroy.[9] The results have not been altogether uniform, and the accuracy of the method as applied to blood is questionable on account of the necessary reduction of the hemoglobin, and the influence of the protein substances present.

The fact that the gas chain method of determining the pH of the blood requires a delicate and expensive piece of physicochemical apparatus as well as considerable technical training has been standing in the way of clinical investigations of acidosis directly from the side of the blood, and has led to the very valuable but indirect methods of approach, such as those utilized in the studies of Sellards,[10] Palmer and Henderson[11] and Adler and Blake.[12]

## PRINCIPLE OF THE METHOD

Heretofore the indicator method has not proved of great value in the studies of hydrogen-ion concentration of the blood, although the reaction of inorganic solutions may be determined quite accurately by this means.[13] Different indicators show their color changes at varying degrees of hydrogen-ion concentration; for example, the color of methyl orange changes from pink to yellow as the pH of its solution changes from 3 to 5. At intermediate points, various colors may be obtained and a certain color indicates a definite pH. Similarly, phenolphthalein changes from colorless to pink between pH8 and pH10 and can be used for the measurement of H-ion concentrations between these two points. In carrying out the indicator method, it is necessary to have a series of standard solutions of known pH and an indicator exhibiting easily distinguishable color changes at hydrogen-ion concentrations approximating that of the solution under consideration. It is then simply necessary to add equal amounts of indicator to the standard solutions and to the solution being tested and to determine which of the colors in the standard solutions most closely matches that of the unknown solution.

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6. Hasselbalch and Lundsgaard: Biochem. Ztschr., 1912, xxxviii, 77. Lundsgaard: Ibid., 1912, xli, 247.
7. Peters: Physiol. Soc. Prac., January, 1914.
8. Peabody, F. W.: Studies on Acidosis and Dyspnea in Renal and Cardiac Disease, THE ARCHIVES INT. MED., 1914, xiv, 236.
9. Milroy: Quart. Jour. Exper. Physiol., 1914, viii, 141.
10. Sellards: Johns Hopkins Hosp. Bull., 1912, xxiii, 289; ibid., 1914, xxv, 101.
11. Palmer, W. W., and Henderson, L. J.: Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, THE ARCHIVES INT. MED., 1913, xii, 153.
12. Adler, H. M., and Blake, Gerald: The Retention of Alkali by the Kidney with Special Reference to Acidosis, THE ARCHIVES INT. MED., 1911, vii, 479.
13. For a full description of the application of indicators to this purpose, see Sörensen: Ergebn. d. Physiol., 1912, xii, 393.

This method has been successfully used on the urine by Henderson[14] and by Walpole.[15] As proteins interfere with the colors of many indicators, and as both blood and serum possess color, it has been impossible to apply the method directly to the blood.[16]

It seemed probable that the indicator method might be utilized for blood, provided coloring matters and proteins could be excluded by means of dialysis.[17] If blood is dropped into collodion sacs and dialyzed for five minutes, the dialysate is free from proteins and coloring matter, but contains salts, and is well adapted to the use of indicators.

Since phenolsulphonephthalein exhibits definite variations in quality of color, with very minute differences in hydrogen-ion concentration between pH6.4 and 8.4, it was adopted as the indicator in this method.

### PREPARATION OF STANDARD COLORS

Standard phosphate mixtures are prepared according to Sörensen's[18] directions as follows:

1/15 mol. acid or primary potassium phosphate. 9.078 grams of the pure recrystallized salt ($KH_2PO_4$) is dissolved in freshly distilled water and made up to 1 liter.

1/15 mol. alkaline or secondary sodium phosphate. The pure recrystallized salt ($Na_2HPO_4 . 12H_2O$) is exposed to the air for from ten days to two weeks, protected from dust. Ten molecules of water of crystallization are given off and a salt of the formula $Na_2HPO_4 . 2H_2O$ is obtained; 11.876 grams of this is dissolved in freshly distilled water and made up to 1 liter. The solution should give a deep rose red color with phenolphthalein. If only a faint pink color is obtained, the salt is not sufficiently pure.

The solutions are mixed in the proportions indicated below to obtain the desired pH:

| pH | 6.4 | 6.6 | 6.8 | 7.0 | 7.1 | 7.2 | 7.3 | 7.4 | 7.5 | 7.6 | 7.7 | 7.8 | 8.0 | 8.2 | 8.4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary Potas. Phos., c.c. | 73 | 63 | 51 | 37 | 32 | 27 | 23 | 19 | 15.8 | 13.2 | 11.0 | 8.8 | 5.6 | 3.2 | 2.0 |
| Secondary Sodium Phos., c.c. | 27 | 37 | 49 | 63 | 68 | 73 | 77 | 81 | 84.2 | 86.8 | 89.0 | 91.2 | 94.4 | 96.8 | 98.0 |

Three c.c. of each of the solutions are placed in suitable small test tubes (100 × 10 mm., inside measurement). Five drops of an aqueous

14. Henderson: Biochem. Ztschr., 1910, xxiv, 40.

15. Walpole: Biochem. Jour., 1910, v, 207.

16. Sörensen (Biochem. Ztschr., 1909, xxii, 238) has applied the indicator method to the filtrate obtained after precipitating blood or serum by boiling with three volumes of dilute hydrochloric acid. Adler (Am. Jour. Physiol., 1907, xix, 1) has tested the reaction of the serum with paper dyed pink with rosolic acid. The objections to these methods are obvious.

17. Preliminary experiments showed that it was impossible, by the indicator method, to obtain concordant results on dilutions of serum.

18. Sörensen: Biochem. Ztschr., 1909, xxii, 352.

0.01 per cent. solution of phenolsulphonephthalein are added to each tube. The tops are sealed off. The series of colors, representing different concentrations of hydrogen ions, constitutes the standards for comparison of color in carrying out the determination.[19]

### PREPARATION OF SACS

One ounce of celloidin (Anthony's negative cotton)[20] is dissolved in 500 c.c. of a mixture of equal quantities of ether and ethyl alcohol. The solid swells up and dissolves with occasional gentle shakings, in forty-eight hours. As a small amount of brown sediment separates out at first, the solution should stand for at last three or four days, after which the clear supernatant solution is ready for use.[21] A small test tube (120 by 9 mm. inside measurement) is filled with this mixture, inverted, and half the contents poured out. The tube is then righted, and the collodion allowed to fill the lower half again. A second time it is inverted and rotated on its vertical axis, the collodion being drained off. Care must be taken to rotate the tube, in order to secure a uniform thickness throughout. The tube is clamped in the inverted position and allowed to stand for ten minutes, until the odor of ether finally disappears. It is filled five or six times with cold water, or it is allowed to soak five minutes in cold water. A knife blade is run around the upper rim, so as to loosen the sac from the rim of the test tube, and a few cubic centimeters of water are run down between the sac and the glass of the tube. By gentle pulling the tube is extracted, after which it is preserved by complete immersion in water.[22]

### THE SALT SOLUTION USED IN THE METHOD

The blood or serum is dialyzed against an 0.8 per cent sodium chlorid solution.

Before applying the test, it is necessary to ascertain that the solution is free from acids other than carbonic. To determine this, a few cubic centimeters of the salt solution are placed in a Jena test tube and one or two drops of the indicator added, whereupon a yellow color appears. On boiling, carbon dioxid is expelled, and the solution loses its lemon color and takes on a slightly brownish tint. In the absence of this change, other acids are present, and the salt solution is therefore not suitable.[23] If, on the other hand, on adding the indicator, pink at once appears, the solution is alkaline and hence cannot be used.

### TECHNIC OF METHOD

The technic can be carried out on either serum, plasma, whole or defibrinated blood. The work must be done in a room free from fumes of acids or ammonia.

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19. The colors may fade slightly in a month's time, but may still be used for comparison if less indicator is added to the "unknown" solution, as the color quality remains the same.

20. Obtained from the Ansco Co., Binghamton, N. Y. This contains 30 per cent. of water and must be rinsed with absolute alcohol before being dissolved for use.

21. Better sacs are obtained from solutions that have been allowed to "age" in well-stoppered bottles for from two to three weeks.

22. Sacs that have dried became brittle and impervious.

23. It is advisable to keep the salt solution in a Jena glass flask and to protect it from acids in the air by means of a soda lime tube.

One to three c.c. of clear serum[24] or of blood is run, by means of a blunt pointed pipet, into a dialyzing sac which has been washed inside and outside with salt solution and which has been tested for leaks by filling with the salt solution.[25] The sac is lowered into a small test tube (100 by 10 mm., inside measurements) containing 3 c.c. of the salt solution, until the fluid on the outside of the sac is as high as on the inside. From five to ten minutes are allowed for dialysis.[26] The collodion sac is removed and 5 drops of the indicator are thoroughly mixed with the dialysate. The tube is then compared with the series of standards until the corresponding color is found, which indicates the hydrogen-ion concentration present in the dialysate.

These tests have been carried out with 3 c.c. of blood or serum. The same results are obtained with 1 c.c. of blood or serum on the inside of the sac, and with this amount it is immaterial whether there is 1 or 3 c.c. of salt solution on the outside.

### COMPARISON OF TUBES WITH STANDARDS

For this, a good light (natural or artificial) and a white background are requisites. Readings must be made immediately. The tube matching[27] most closely is selected and also the tubes on either side of it. These are critically inspected against a white background. Changing the order of the tubes often makes differences more apparent.[28]

### CONTROLS OF THE METHOD

Repeated duplicate determinations on the same samples of blood and of serum have convinced us that the limits of error are very slight: for example, the serum from a case of mild acidosis (using quantities of serum varying from 1 to 3 c.c. and dialyzing for from five to fifteen minutes) gave the following series of readings: 7.55, 7.55, 7.55, 7.55, 7.6, 7.55, 7.55, 7.55, 7.55, 7.55. The oxalated whole blood from the same case gave the following readings under similar conditions: 7.25, 7.25, 7.25, 7.25, 7.2, 7.25, 7.25, 7.3, 7.25, 7.25, 7.25, 7.25, 7.25, 7.25.

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24. Hemolysis tends to increase the acidity and must be avoided.

25. A sac may be used more than once for serum, provided it is thoroughly washed.

26. The alkalinity of the dialysate increases rapidly during the first five minutes. There is no appreciable change during the next ten minutes. Proteins may make their appearance in the dialysate in from ten to twenty minutes.

27. It must be borne in mind that one is here matching the quality of color and not intensity as in ordinary colorimetry.

28. A color falling between two of the standards may be read, by interpolation, to another decimal place. No effort was ever made to read closer than 0.05. Duplicate determinations should be made in all cases when sufficient material is available.

In order to test out the effect of the variations in the sacs used, a number of determinations were made on the same sample of serum with the following results: ordinary thin sac, 7.7; thick sac, 7.7; opaque, irregular sac, 7.7; ordinary thin sac, 7.65; very thick sac, 7.7. A series of six normal serums were run through, 3 c.c. and 1 c.c. portions being used for dialysis. In every instance identical readings were obtained.

### APPLICATION OF THE METHOD

Having thus assured ourselves of the accuracy of the method, a series of bloods from normal and pathologic cases were studied, with the following results:

1. *Normal individuals;* twenty-five cases. (*a*) Serum; Twenty-four of the twenty-five cases read between 7.6 and 7.8. In one instance, 7.9 is recorded:

| pH | Cases |
|---|---|
| 7.6 | 4 |
| 7.65 | 1 |
| 7.7 | 5 |
| 7.75 | 5 |
| 7.8 | 9 |
| 7.9 | 1 |

(*b*) Whole blood (oxalated[29]); nineteen determinations. These all read between 7.4 and 7.6:

| pH | Cases |
|---|---|
| 7.4 | 3 |
| 7.45 | 2 |
| 7.5 | 4 |
| 7.55 | 5 |
| 7.6 | 5 |

The slightly greater acidity of whole blood as compared with serum has been recognized by almost all investigators in this field, and appears to be due to the fact that hemoglobin, and especially oxyhemoglobin, behaves as a weak acid.

(*c*) Defibrinated blood. Early in the course of the work, defibrinated blood was run in parallel series with serum and oxalated whole blood. It was found that in general, the results tended to correspond to those obtained with the whole blood, but the range of variation was rather wide: from 7.4 to 7.8. No additional information was obtained, and the defibrination merely served to complicate the procedure. Hence it was decided to abandon the use of defibrinated blood in the subsequent course of the investigation.

2. *Miscellaneous medical cases.* In order to determine whether the hydrogen-ion concentration of the blood varies from the normal in disease, a rather large variety of conditions was studied. Sixty-three

29. The blood was collected in tubes containing a little dry powdered sodium oxalate (free from carbonate).

determinations were made in 52 cases, comprising the following conditions: nephritis (acute and chronic), 12 cases; diabetes mellitus, 8 cases; myocardial insufficiency, 5 cases; syphilis, 4 cases; chronic arthritis, 3 cases; pernicious anemia, 2 cases; neuroses, 3 cases, and 1 case each of pyelitis, empyema, carcinoma of neck, hemorrhoids, typhoid fever, pneumonia, meningococcus meningitis, tuberculous meningitis, cholelithiasis (jaundice), pulmonary edema, cerebral hemorrhage (coma), tuberculous pleurisy, foot and mouth disease, angioneurotic edema and brain tumor.

The results were as follows:

(*a*) Serum; sixty-three determinations. Sixty of the sixty-three determinations read between 7.6 and 7.8:

| pH | Cases |
|---|---|
| 7.6 | 14 |
| 7.65 | 4 |
| 7.7 | 19 |
| 7.75 | 1 |
| 7.8 | 22 |

The three exceptions not coming within these limits were:

(1) An instance of traumatic neurosis with a reading of 7.9. (2) A febrile typhoid with a reading of 8.0. (3) A case of chronic nephritis with hematemesis from an acute gastric ulcer, whose serum after the transfusion of 850 c.c. of blood, by the syringe method, gave a reading of 7.95.

(*b*) Whole blood (oxalated); thirty-three determinations, of which thirty-one read between 7.4 and 7.6:

| pH | Cases |
|---|---|
| 7.4 | 1 |
| 7.45 | 2 |
| 7.5 | 10 |
| 7.55 | 8 |
| 7.6 | 10 |

The two exceptions were instances of pernicious anemia. The first case, immediately following transfusion, gave a reading of 7.7 on the whole blood, this being identical with that on the serum. It is of interest to note that before transfusion the readings on the serum and whole blood were also the same, that is, 7.6. The second case gave a reading of 7.65 in the whole blood, this again being identical with that on the serum.

3. *Acidosis.* From the preceding paragraphs it is evident that the hydrogen-ion concentration of the whole blood or serum, normally and in a great variety of disease conditions, is not subject to great variations. A small series of cases with clinical or laboratory evidence of acidosis (or both) has been studied, the results appearing in Table 1. Fifteen determinations were made in eight cases.[30]

30. Detailed clinical histories are appended at the end of this paper.

TABLE 1.—Acidosis (Eight Cases, Fifteen Determinations)

| Case No. | Date | H-Ion Concentration | | Diagnosis and Remarks |
|---|---|---|---|---|
| | | Serum | Whole Blood (Oxal.) | |
| 1 | 12/26/14 | .... | 7.1 | Congenital cystic kidneys; adherent pericardium; myocardial insufficiency; hydrothorax; ascites; uremia; 'phthalein, trace in two hours; $CO_2$ tension of alveolar air, 19.5 mm. Hg. |
| | 1/ 2/15 | 7.4 | .... | Dull; drowsy; 'phthalein, still only a trace in two hours. |
| 2 | 12/ 3/14 | 7.2 | .... | Acute and chronic nephritis; hypertension; uremia; 'phthalein, trace in two hours; Sellards' test, complete decolorization on evaporation. |
| 3 | 1/13/15 | 7.55 | .... | Eclampsia;* mild toxemia. |
| 4 | 1/25/15 | 7.5 | 7.3 | Eclampsia;* severe toxemia. $NH_3$ nitrogen in urine, 18 per cent. |
| | 1/29/15 | 7.8 | 7.5 | Thirty-six hours after labor; alkali therapy; doing well. |
| 5 | 1/18/15 | 7.2 | .... | Sarcoma of kidney and antrum; acidosis; sudden onset of acidosis with "air hunger"; Sellards' test, complete decolorization on evaporation; acetone and diacetic acid in urine. |
| | 1/19/15 | 7.45 | .... | After large doses of alkali; better; Sellards' test, faint pink color before complete evaporation. |
| | 1/28/15 | 7.8 | .... | More alkali; no dyspnea. |
| | 2/18/15 | 7.3 | .... | Respirations again deep and noisy; acetone in urine. |
| 6 | 1/22/15 | 7.5 | .... | Recurrent vomiting; no food retained for three days; acetone and diacetic acid in urine. |
| 7 | 1/22/15 | 7.4 | .... | Alimentary intoxication. |
| | 1/22/15 | 7.55 | .... | After alkali therapy; death next day. |
| 8 | 1/ 8/15 | 7.4 | .... | Acute and chronic nephritis; myocardial insufficiency (slight); anasarca; dyspnea; 'phthalein, 55 per cent. in two hours; acetone in urine. |
| | 1/20/15 | 7.6 | 7.5 | Much improved; $CO_2$ tension of alveolar air, 40.1 mm. Hg. |

* We are indebted to Dr. J. Whitridge Williams for permission to study these cases occurring in his service.

### CHANGES IN THE HYDROGEN-ION CONCENTRATION OF THE BLOOD IN EXPERIMENTAL CONDITIONS

An effort has been made to see if similar changes in the pH of the blood and serum can be demonstrated in experimental acidosis in dogs. Animals were injected intravenously with dilute hydrochloric acid. Protocols of two experiments are given in Tables 2 and 3.

TABLE 2.—PROTOCOL OF EXPERIMENT 1.—INTRAVENOUS INJECTION OF N/3 HYDROCHLORIC ACID INTO A DOG* (FEMALE, WEIGHT 7.3 KG.)

| Time p. m. | Amt. of HCl Injected c.c. | H-Ion Concentration | | | Remarks |
|---|---|---|---|---|---|
| | | Serum | Whole Blood (Oxal.) | Blood Drawn Directly Into Sac | |
| 3.43 | .. | 7.75 | 7.6 | 7.55 | |
| 3.44-3.49 | 50 | .... | .... | .... | |
| 4.00 | .. | 7.65 | 7.4 | 7.45 | Breathing normally. |
| 4.14 | .. | 7.7 | 7.45 | .... | |
| 4.17-4.23 | 40 | .... | .... | .... | |
| 4.26 | .. | 7.6 | 7.5 | 7.4 | No essential change in condition. |
| 4.50-4.56 | 30 | .... | .... | .... | Toward end of injection, respirations slow and deep, 14 per minute. |
| 5.00 | .. | 7.65 | 7.55 | 7.5 | Marked "air hunger"; respirations, 11 per minute; pulse, 31 to ¼; regular. |
| 5.03 | .. | .... | .... | .... | Respirations still slow but shallower; animal in fairly good condition. |
| 5.21-5.30 | 40 | .... | .... | .... | At 5.26 respirations 11 per minute. |
| 5.45 | .. | 7.45 | 7.45 | 7.4 | Restless; struggling. |
| 5.50 | .. | .... | .... | .... | Off table; no "air hunger"; lying down in no apparent discomfort; recovered. |

* Injections made in part into jugular, in part into leg vein. Blood for examination withdrawn either from jugular or leg vein on opposite side. HCl made up in 0.8 per cent. salt solution.

### GENERAL DISCUSSION

In order to determine the actual hydrogen ion concentration of the blood as it exists in the body, it is necessary that measurements be made at body temperature and under the carbon dioxid tension existing in the vessels as shown by analysis of the alveolar air. Most of the published results do not fulfil these two requirements and therefore do not give the reaction, as Lundsgaard[31] expresses it, *strictissimo sensu*.

31. Lundsgaard: Biochem. Ztschr., 1912, xli, 247.

In a study of acidosis, however, these considerations are of academic rather than of clinical importance, since we are concerned with variations in the pH rather than with its actual value.

The more recent electrometric measurements have been carried out at the carbon dioxid tension existing in the alveolar air and in most cases at room temperature (18 C.). So long as the measurements are made at a constant tension of carbon dioxid and at a constant temperature, the results are of value for comparative purposes.

TABLE 3.—Protocol of Experiment 2.—Intravenous Injection of N/2 Hydrochloric Acid Into a Dog (Female, Weight 7 Kg.)

| Time | Amt. of HCl Injected | H-Ion Concentration | | Remarks |
|---|---|---|---|---|
| | | Serum | Whole Blood (Oxal.) | |
| 3.21 | .... | 7.7 | 7.55 | Serum light yellow; clear. |
| 3.28 | Injection begun. | .... | .... | |
| 3.36 | .... | .... | .... | Beginning to breathe deeply and slowly; heart's action very forceful; regular. |
| 3.50 | 90 c.c. have been injected. | 6.9 | 6.9 | "Air hunger" marked; respirations, 28 per minute. Heart's action forceful; regular; serum shows moderate amount of hemolysis. |
| 3.56 | Injection ended; 105 c.c. have been injected. | .... | .... | |
| 4.00 | .... | 6.9 | 6.9 | In extremis; gasping for breath; heart still beating strongly; serum shows marked hemolysis. |
| 4.09 | .... | .... | .... | Ceased breathing; heart stopped beating; artificial respiration and intravenous injection of 5 per cent. solution of sodium bicarbonate unavailing. |

In the method described in this paper, blood is exposed to the air so that the carbon dioxid tension is low, but apparently, fairly constant. The objection might be made that the pH would depend on the amount of carbon dioxid which has escaped from the blood or serum. The following experiments indicate, however, that the pH is not dependent, within reasonable limits, on the time elapsing between the taking of the blood and the determination of the pH, provided the

tube containing blood is kept stoppered and on ice, as will be seen from the following:

| | Serum | Oxalated Blood |
|---|---|---|
| Immediately ..... | 7.75 | 7.55 |
| After 2½ hours ..... | 7.75 | 7.55 |
| After 19 hours ..... | 7.75 | 7.55 |
| After 24 hours ..... | 7.75 | 7.55 |

If, however, blood is drawn directly into a sac immersed in a tube of salt solution and the reading compared with that from the blood drawn and determined in the usual manner, slight variations are encountered (see Experiment 1).

By thoroughly shaking the blood or serum in the air, its alkalinity is increased. Therefore, shaking should, in general, be avoided, unless it is desired to determine the pH at a zero $CO_2$ tension. Such studies have been carried on by Dr. D. W. Wilson.

The influence of the temperature on the readings has been determined, and the results appear in the accompanying tabulation.

TABLE 4.—Variations in Hydrogen Ion Concentration Due to Changes in Temperature

| | A | | B | |
|---|---|---|---|---|
| Temperature | Serum | Whole Blood (Oxal.) | Serum | Whole Blood (Oxal.) |
| 20 C. | 7.75 | 7.55 | 7.75 | 7.45 |
| 30 C. | 7.85 | 7.5 | 7.8 | 7.4 |
| 37 C. | 7.9 | 7.65 | 7.9 | 7.45 |

This effect of temperature has been recognized by previous workers. It is evident that in order to obtain comparable results, temperature control is necessary. Our measurements have been made between 20 and 24 C.

The dialysate of the blood or serum is slightly more acid than the original material, if one can judge from experiments carried out with dilute sodium bicarbonate solutions containing carbon dioxid, and phosphates of approximately the pH and concentration of blood. That the variation is a constant one under the conditions of the method is shown by the close agreement of duplicate determinations, which has been referred to previously in this paper.

By a coincidence, the results obtained from the dialysate from the whole blood and from serum correspond very closely to those obtained directly by the electrical method when the latter measurement is made at 18 C. and at a carbon dioxid tension of 40 mm. Hg.

This agreement in results is probably due to the antagonistic character of the two main sources of error involved in the method of dialysis, namely, loss of carbon dioxid tending to give higher, that is, more alkaline readings, and disproportionate dialysis of acid and basic constituents yielding lower, that is, more acid readings. For clinical pur-

poses, particularly the study of acidosis, the method of dialysis is quite as applicable as the electrometric method, and yields results in general comparable with those of that method. It has the advantages of simplicity and rapidity.

## CONCLUSIONS

1. The indicator method of determining H-ion concentration is made applicable to blood and serum by utilization of dialysis through a collodion membrane, which excludes the disturbing influences of color and of proteins. The method is simple, accurate, rapid and well adapted for clinical use.

2. The technic consists of dialyzing 3 c.c. of blood or serum at room temperature against 3 c.c. of 0.8 per cent. salt solution for five minutes, adding an indicator and comparing with colored standard phosphate mixtures of known H-ion concentration.

3. Phenolsulphonephthalein is employed as the indicator in this method. It is found to exhibit easily distinguishable variations in quality of color, with minute differences in H-ion concentration between the limits pH6.4 and pH8.4.

4. Oxalated blood from normal individuals gives a dialysate with a pH varying from 7.4 to 7.6, while that of serum ranges from 7.6 to 7.8.

5. Variations from these figures toward the acid side were encountered only in conditions which clinically, and from the standpoint of the laboratory findings, evidenced an acidosis.

6. In a small series of clinical acidoses, the serums varied from 7.55 to 7.2 and the oxalated blood from 7.3 to 7.1. In experimental acidosis in dogs, a pH of 6.9 has been encountered in both serum and blood just before death.

## REPORT OF CASES

CASE 1.—H. S. (Medical No. 33,441), a white man, aged 43. Diagnosis: congenital cystic kidneys, adherent pericardium, myocardial insufficiency, edema of lungs, hydrothorax, and uremia. Admitted Dec. 12, 1914.

The patient had good general health until ten years ago. He had muscular rheumatism at eight. Eighteen years ago he had an attack of "acute Bright's disease," which confined him to bed for two weeks. Ten years ago, a lump was discovered in the left flank. Exploratory operation revealed congenital cystic kidneys and a few of the cysts in the right kidney were punctured. Five years later the left kidney also became palpable.

The present illness began five months before the patient's admission, with attacks of nocturnal dyspnea, which gradually became worse. Three weeks ago swelling of the legs appeared.

Examination showed an undernourished man, dyspneic and orthopneic. Signs of fluid were present in both pleural sacs, with bubbling râles over the lower lobes. There was marked cardiac enlargement and systolic retraction of interspaces lateral to apex. Broadbent's sign was present, also a protodiastolic gallop. There was a faint systolic blow at the apex, which was transmitted to the axilla. The pulmonic second sound was accentuated. The abdomen was

distended with fluid. A large mass covered with bosses was palpable in each flank. The liver was enlarged and tender. Edema of legs was noted.

Repeated phenolsulphonephthalein tests showed the excretion of only a trace in two hours.

The $CO_2$ tension of alveolar air was: December 16, 23.3 mm. Hg; December 18, 19.1 mm. Hg.

The hydrogen-ion concentration of blood was: December 26, whole blood, 7.1; January 2, serum, 7.4.

The nonprotein nitrogen of the blood was 118 mg. per hundred cubic centimeters. The blood pressure ranged from 155 to 135 mm. Hg systolic, 110 to 75, diastolic.

The urine was pale and clear with a specific gravity of 1.008 to 1.012. A trace of albumin and hyaline casts were observed. Acetone was present on several occasions. The patient was discharged Jan. 11, 1915, somewhat improved.

CASE 2.—C. O. P. (Medical No. 33,385), a white man aged 43. Diagnosis: arteriosclerosis, acute and chronic nephritis, hypertension and uremia. Admitted Dec. 1, 1914. The patient had syphilis twenty years ago and was treated by intermittent courses of mercury for four years. He had uncomplicated typhoid fever twenty-three years ago and from 1908 to 1912 drank heavily.

The present illness began two years ago with severe headaches, usually coming on in the early morning hours and becoming gradually more severe. Polyuria and nycturia soon followed. Three months ago he had an attack of sudden loss of consciousness with a generalized convulsion lasting five or six minutes, and followed by profuse vomiting. He was in bed for four days. There was no paralysis. Eight weeks before his admission blood was discovered in the urine. He was put to bed and has remained there since. Two months ago his eyesight began to fail; he is now unable to read.

Examination showed a fairly nourished man with pasty complexion and decidedly anemic appearance. The heart was moderately enlarged. There was a presystolic gallop, with numerous extrasystoles. The second aortic sound was loud and ringing. The radials and brachials were diffusely thickened; the temporals tortuous and sclerosed. Advanced albuminuric retinitis was noted, with fresh hemorrhage in both eyes.

The blood count showed red blood cells, 3,520,000; white blood cells, 11,400; hemoglobin (Sahli) 65 per cent.

By the phenolsulphonephthalein test, excretion in two hours on numerous occasions ranged from a trace to 16 per cent. December 3, the patient was vomiting and belching at frequent intervals and was very drowsy.

Sellard's test on the blood serum showed complete decolorization on evaporization; no color on addition of water.

The hydrogen-ion concentration of the serum was 7.2. During the patient's stay in the hospital the blood pressure ranged from 208 to 174 systolic; 136 to 108 diastolic.

The urine in quantity was 1,025 to 5,025 c.c. in twenty-four hours; its specific gravity, 1.005 to 1.009. Smoky at first, it became clear with the polyuria, then bloody again. From 2 to 5 grams of albumin per liter were present. Hyaline, granular and blood casts were observed. The patient refused to remain for treatment and was discharged unimproved, Dec. 22, 1914.

CASE 3.—F. W. (Obstetrical Service), a colored girl, aged 18, was admitted Jan. 8, 1915. Diagnosis: pre-eclamptic toxemia; postpartum eclampsia. The girl was nine months pregnant. On the day before admission, albumin and casts were found in the urine, and the patient was advised to enter the hospital. During the course of the next few days she complained of epigastric discomfort and frontal headaches of increasing severity. The systolic blood pressure was 190 mm. Hg. On January 12, slight edema of the legs appeared.

On January 13, at 7:55 a. m., spontaneous labor occurred. Ten minutes after the birth of the child the patient had a typical eclamptic convulsion of moderate

severity lasting two minutes. The blood pressure (systolic) at this time was 150 mm. Hg. There were two more convulsions that day. Following bleeding, purging and sweating, a normal convalescence ensued.

The hydrogen-ion concentration of the serum obtained at venesection was 7.55.

The nonprotein nitrogen in the blood was 42 mg. per 100 c.c.

January 24, the phenolsulphonephthalein test showed 55 per cent. excretion in two hours.

The ammonia nitrogen in the urine:

January 13 = 5 per cent.
January 14 = 9 per cent.
January 16 = 7 per cent.

CASE 4.—M. K. (Obstetrical Service), a white woman, aged 19, was admitted Jan. 25, 1915. Diagnosis: eclampsia; spontaneous labor.

The patient was a strong, well-nourished primipara, nine months pregnant. The pregnancy had been uneventful until the morning of January 25, when, at 4 a. m., she began to have severe headache, nausea and vomiting. Shortly afterward she had one convulsion. When seen in the out-patient service she was conscious but drowsy. Blood pressure (systolic) was 150 mm. Hg; the pulse 80 per minute. The urine showed 8 grams of albumin per liter.

She was admitted to the ward at 7 p. m., unconscious, exceedingly restless, and having typical, moderately severe eclamptic convulsions at intervals of three-quarters of an hour. The blood pressure (systolic) was 180 mm. Hg. There was no dyspnea and very slight edema of lower legs. She had seven convulsions in all, the last occurring at 5 a. m. on the morning of January 26. Blood for hydrogen-ion determination, obtained after the third convulsion, gave a reading of 7.5 on the serum; 7.3 on the whole blood.

Following venesection, purgation and sweating, and the administration of 40 grams of sodium bicarbonate by stomach-tube, the convulsions finally ceased and consciousness returned on the morning of January 26. On January 28 a dead child was born spontaneously. The puerperium was uneventful.

The ammonia nitrogen of the urine during the three days preceding delivery ranged from 18 to 10 per cent.

January 29, the hydrogen-ion concentration of blood was for the serum, 7.8; for the whole blood, 7.5.

CASE 5.—L. C. (Harriet Lane Home No. 6,538), a white boy, aged 3, was admitted Jan. 13, 1915. Diagnosis: sarcoma of the kidney and antrum; acidosis.

The boy had been a normal, healthy child up to three months before admission, when, following a trauma to the face, a small, red swelling appeared on the left cheek, subsequently pushing through to the roof of the mouth. Though painless, this swelling had gradually grown larger.

Examination showed a well-developed, well-nourished child. There was a firm mass in the left cheek, apparently arising in the antrum, and pushing down the left side of the hard palate in the mouth. There was a nodular, firm mass, the size of a man's fist, in the right umbilical region.

January 16: Breathing was rapid and deep.

January 17: There was marked dyspnea; the respirations were 40 per minute

January 18: Respirations unusually deep, with actual "air hunger." The urine contained acetone and diacetic acid.

Sellards' test showed colorless on complete evaporation. The hydrogen-ion concentration of the serum was 7.2. One hundred and seventy-five c.c. of a 5 per cent. solution of sodium bicarbonate was given by the Murphy method. This was followed by 175 c.c. of a 4 per cent. solution of sodium bicarbonate intravenously. After the first 50 c.c., respirations became noticeably less labored, and shortly after the completion of the injection the child was quite comfortable. Small doses of bicarbonate were continued by mouth.

January 19: Sellards' test showed a faint pink color before complete evaporation.

The hydrogen-ion concentration of the serum was 7.45. The child was breathing normally, though mentally rather dull.

During the succeeding weeks several radium treatments were administered and it was believed that the abdominal mass had grown somewhat smaller.

On February 18 the respirations became suddenly deep and noisy. The child seemed drowsy. The urine showed a trace of acetone, but no diacetic acid. The patient was given alkali by mouth.

The hydrogen-ion concentration of the serum was 7.3.

On February 25 the patient was discharged. Breathing again was normal though the general condition was failing.

CASE 6.—A. McK. (Harriet Lane Home), a white boy, aged 6, was admitted Jan. 21, 1915. Diagnosis: recurrent vomiting.

The boy had been a normal child except that he had always had a "weak stomach." Three days before admission, following an indiscretion in diet, he complained of abdominal pain. Next day he began to vomit and since then had not retained any food except a little orange juice. He vomited without any apparent effort, and after vomiting seemed quite well.

Examination showed a sparely nourished child, apparently quite normal in all respects. The urine contained acetone and diacetic acid. The hydrogen-ion concentration of the blood serum was 7.5. Following a well-regulated dietary regimen, he rapidly improved and went home.

CASE 7.—V. D. (Harriet Lane Home No. 6,628), a white girl, aged 2 months, was admitted Jan. 22, 1915; died Jan. 23, 1915. Diagnosis: alimentary intoxication.

The patient was a full-term, apparently healthy, child. Sixteen days before admission she began to vomit after every feeding and had frequent green stools. The vomiting and diarrhea persisted up to the time she was brought to the hospital.

Examination showed a small, moderately well-nourished baby, conscious and crying fretfully. Slight cyanosis was present. The respiratory rate was increased, the respirations being full and deep. White blood cells, 22,170. The stool, large, green and watery, contained mucus and food residue.

Sellards' test showed no color on evaporation or on addition of distilled water after evaporation.

The hydrogen-ion concentration of the serum was 7.4.

Intensive alkali therapy was given, both intravenously and subcutaneously. The respirations improved a little, becoming shallower. There was one slight convulsion and constant convulsive twitchings of the face and extremities.

The hydrogen concentration of the serum after intravenous injections of sodium bicarbonate was 7.55.

The respirations gradually became shallower and more infrequent and the baby died at 4:55 a. m. on January 23. There was complete anuria during the stay in the hospital. Partial necropsy showed only enlargement of the mesenteric lymph nodes.

CASE 8.—M. F. (Medical Service), a white man, aged 20, was admitted Jan. 7, 1915. Diagnosis: acute and chronic nephritis, hypertension, and myocardial insufficiency.

The patient had frequent sore throats. Eighteen months ago he began to have morning headaches. For three months, dyspnea on exertion was noted, becoming progressively more marked. Six days before admission the feet and ankles began to swell, and the abdomen and face have since become edematous. Anorexia, dizzy spells and epistaxis have occurred during the past week.

Examination showed an overnourished young man, dyspneic, sallow and pale. Marked oral sepsis was present; the tonsils were large and ragged. Crepitant râles were heard at the left base. The heart was markedly enlarged.

There was a snapping aortic second sound. The liver was enlarged and tender. Edema of feet and ankles was present. There was a moderate secondary anemia.

The Wassermann test was negative.

The phenolsulphonephthalein test showed 55 per cent. of excretion in two hours. The hydrogen-ion concentration of the serum was 7.4. The nonprotein nitrogen of the blood was 36 mg. per 100 c.c.

January 20: The hydrogen-ion concentration of the serum was 7.6; whole blood, 7.5. The $CO_2$ tension of alveolar air was 40.1 mm. Hg.

The urine in quantity was 1,500 to 2,000 c.c. in twenty-four hours. The specific gravity was 1.012 to 1.013. There were 1.5 to 2.75 grams of albumin per liter. On admission, red blood cells and acetone were observed, which subsequently disappeared. Numerous granular casts were found.

The blood pressure ranged from 170 to 130 mm. Hg systolic; 110 to 65 diastolic. The patient is somewhat improved. He is still in the hospital (April, 1915).

# THE ROENTGENOLOGIC DETERMINATION OF GASTRIC MOTILITY

## WITH A COMPARISON OF THE RESULTS OBTAINED IN A SERIES OF CASES EXAMINED BOTH BY THE ROENTGEN RAY AND THE TEST-MEAL *

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The testing of gastric motility by roentgenologic methods has been of such striking and practical value that it seems worth while to report the results obtained in a considerable series of operated cases and to compare them with the findings gained by the test-meal and stomach tube. We have subjected approximately 10,000 patients to the Roentgen test, but have selected for tabular analysis and comparison those cases seen during the year 1914. In 1914, 4,118 patients were examined by the Roentgen ray for gastro-intestinal disease. Of this number 1,140 were operated on. In 950 of them a motor-meal test was also made by the gastro-enterologist and the tabulation is based on these 950 cases.

Before discussing the results it may be well to recall some of the elementary facts as to the physiology and pathology of the gastric motor function and recount some of the principal tests for disturbance in this respect.

It is almost superfluous to offer here a reminder of the magnificent work of William Beaumont, but so many of his conclusions remain uncontradicted to this day and the inspiration which he gave to accurate methods of observation have so strongly influenced our present conceptions that some of his findings with respect to motility require repetition. For example, his deduction[1] that "the time required for the digestion of food is various, depending upon the quantity and quality of the food, state of the stomach, etc.; but that the time ordinarily required for the disposal of a moderate meal of the fibrous parts of meat, with bread, etc., is from three to three and a half hours." Further, he drew the "inference," as he expressed it, "that oily food is difficult of digestion" and that "water, ardent spirits and most other fluids are not affected by the gastric juice, but pass from the stomach as soon as they are received."

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1. In the Life and Letters of Dr. William Beaumont, by Jesse S. Myer. St. Louis, C. V. Mosby Co., 1912, p. 201.

Cannon[2] also, by his painstaking experiments on animals, has given us reliable data, among which may be summarized the following: The chyme does not pass through the pylorus at the approach of every peristaltic wave but emerges occasionally, at irregular intervals, of from ten to eighty seconds. Acid above opens and acid below closes the pylorus. Fats when given are almost invariably present in the stomach during seven hours observation. Water begins to enter the intestine almost as soon as it enters the stomach. Carbohydrates go through rapidly; proteins more slowly. When carbohydrates and proteins are given one after another the early rate of evacuation is largely the same as that of the first food given. Mixtures of carbohydrates and proteins have an emptying rate intermediate between that of carbohydrates and that of proteins. Fat retards the exit of either foodstuff from the stomach into the intestine. As to consistency of food materials, there is a marked retardation of the outgo of food from the stomach when hard particles are present. Considerable amounts of gas in the stomach retard the discharge of food. Rage, distress, anxiety, grief, anger and violent emotions have a depressive effect on gastric motor activities.

Besides the physiologic variations to which the gastric clearance time is subject, it may also undergo numerous pathologic alterations, in the direction either of an exaggeration or a diminution of motility. Thus we are familiar with the shortened gastric evacuation time of nonobstructive duodenal ulcer and of nonobstructive cancer of the stomach. On the other hand, we are equally familiar with the retarded emptying resulting from so-called atony of the stomach, hyperacidity, and reflex spasm of the pylorus, the latter either from an extrinsic cause, such as disease of the gallbladder, or from an intrinsic cause, such as gastric ulcer. Further, and more importantly, we are acquainted with the gastric retention produced by organic stenoses at or near the pylorus.

Now it would seem that by no simple test can sharp and constant lines of demarcation be drawn between hypermotility, normal motility and hypomotility. Nevertheless, extreme variations in either direction, more especially toward hypomotility, have high diagnostic significance, can be determined at least broadly, and efforts at such determination cannot safely be neglected. The method in most common vogue of testing gastric motility is the administration of a meal and the use of the stomach tube to ascertain whether food remnants are present after the lapse of a certain time. The following citations will give a fair idea of this method.

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2. Cannon, W. B.: The Mechanical Factors of Digestion. New York, Longmans, Green & Co., 1912, p. 84.

Kemp[3] remarks that the impairment of the motor power is fully as important, if not more important in many cases than damage to the secretory functions. He describes various test-meals used in gastric analysis including those of Riegel,[4] Ewald,[5] and Leube[6] and the test-breakfast of Ewald-Boas.[7] Regarding the specific question of motility he states:

> If five hours after a test meal, a small amount of chyme is aspirated the motor power is good. If large quantities are found six hours after the meal the motor function is absolutely (or, if stenosis, relatively) decreased. . . . Some employ the test breakfast. Two hours later the stomach should be empty. If 100 c.c. or more are found at the end of an hour, or varying quantities at the end of two hours, it shows different degrees of motor insufficiency. The test-meal is more accurate. I sometimes administer a test-supper and aspirate in the morning to test the motor function, following immediately with the test breakfast to examine the secretory function.

He also describes without comment the motility tests with salol (Ewald and Sievers[8]), iodopin (Heichelheim[9]) and oil (Klemperer[10]).

Bassler[11] mentions as of value the Leube-Riegel test-dinner, consisting of beef-broth, 400 c.c.; beef, 150 gm.; puree or mashed potatoes, 50 gm.; and a roll of wheat bread. The exit of this meal from the normal stomach should occur within five hours. But he goes on to say:

> A word of caution should here be given in assuming the existence of pathologic conditions when five or six hours afterward small quantities of food are extracted, for, while the great bulk of the meal is gone, tarrying remnants of food may be present even in the perfectly normal stomach up to the sixth and even the seventh hour after the time of ingestion. If at the sixth, seventh or eighth, and so on, hour of extraction after the taking of a mixed meal, considerable quantities of the meal constituents are obtained from a stomach, the existence of the following conditions should be considered, namely: Pyloric obstruction, states of atony, a more or less low state of digestive disturbance from degrees of subacute and chronic gastritis accompanied with poor stomach function, and the existence of neurotic conditions of a depressing type affecting the entire motility of the organ. . . . Another form of examination by the extraction of stomach food contents to diagnose pyloric obstruction from

3. Kemp, R. C.: Diseases of the Stomach and Intestines. Philadelphia, W. B. Saunders Company, 1911, p. 122.

4. Riegel's test-dinner: Meat broth, about 400 c.c.; beefsteak, 150 to 200 gm.; mashed potatoes, 50 gm.; and a roll (35 gm.)

5. Ewald's test-meal: Finely chopped meat, 175 gm.; stale bread, 35 gm.; and butter.

6. Leube's test-meal: A plate of soup, a beefsteak and a roll.

7. Ewald and Boas' test-breakfast: One or two rolls (35-70 gm.); one cup of tea or water (300-400 c.c.); given in the morning in the fasting condition.

8. Ewald and Sievers: Zur Pathologie und Therapie der Magenectasien. Therap. Monatsh., August, 1887.

9. Heichelheim: Ztschr. f. klin. Med., 1900, p. 321.

10. Klemperer: Ueber die Motorische Tatigkeit des Menschlichen Magens, Deutsch. med. Wchnschr., 1888, No. 47.

11. Bassler, A.: Diseases of the Stomach and Upper Alimentary Tract. Philadelphia, F. A. Davis Co., 1913, p. 158.

any cause (particularly its high degree seen in malignancy) should be mentioned. In this the generally employed procedure is to advise the patient to eat a full meal in the early evening, and then to wash out his stomach the following morning — about ten or twelve hours afterward. Should the patient not have vomited during the night, and food remnants be found in the morning, bona fide pyloric stenoses can almost invariably be diagnosed.

He states further that a simplification of this method, which he can indorse as of much value, is the eating of several raisins[12] in the evening and noting if their skins or seeds are obtained in the morning lavage water. While in this test the obtaining of vegetable skins is of much significance a negative result does not always mean that no stenosis exists. A less complete degree of stenosis, particularly in the pyloric region but not directly at the pylorus, may give positive results with the six, seven or eight-hour extraction of the mixed meal, but a negative finding with the raisin-skin method. The matter, he thinks, is entirely one of degree of stenosis; the nearer the stenosis to the pylorus, the more accurate are the results by both methods; the less the degree of the stenosis, or the farther away from the pylorus it is situated, the better is the result from the mixed meal, and the less so from the raisin-skin method.

Einhorn[13] gives a fair summary of gastro-enterologic methods in common use when he says:

The best and easiest way to test the motor function of the stomach is to examine this organ by means of the tube and lavage in the morning in the fasting condition after the ingestion of a substantial supper on the night previous. Normally the stomach is empty, and therefore when the organ is found to contain a quantity of food, this is the best sign of retarded motion.

### ROENTGENOLOGIC TESTS OF MOTILITY

Since the first employment of the Roentgen ray in conjunction with an opaque meal for the diagnosis of gastro-intestinal disease, more or less attention has been directed to gastric motility. By a few men this feature of the examination is considered almost indispensable; by others it is regarded as of secondary importance though usually given some attention, while a few deem it of little moment.

As might be expected, an investigation of the technic used by different roentgenologists shows considerable variance. Wide differences are noted as to:

1. The opaque salt used.
2. The character of the vehicle.

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12. Bassler speaks of this as the "Mayo method." In fairness it should be said, however, that the addition of raisins to the Riegel meal is credited by Cohnheim (Diseases of the Digestive Canal, Edit. 2, Philadelphia, J. B. Lippincott & Co., 1911, p. 35) to Boas and Strauss.

13. Einhorn, M.: Diseases of the Stomach. New York, William Wood & Co., 1911, p. 119.

3. The proportion of opaque material to the medium of suspension.

4. The total quantity administered.

5. Management of the patient with regard to eating after the opaque meal has been taken.

Bismuth subnitrate, which was used in the first examinations of the human digestive tract, produced toxic results in a few instances, and was superseded by bismuth subcarbonate or the carbonate as it is called in Europe. A little later the oxychlorid of bismuth was used to some extent. On the continent a few have employed zirconium oxid. During recent years chemically pure barium sulphate has come into extensive use. So far as we are able to discover from the published observations of others and from our own experience there seems to be little difference in the evacuation time of the various bismuth salts when given under equal conditions; but the difference in this respect between bismuth salts and barium sulphate is marked, the latter leaving the stomach distinctly earlier. Groedel's[14] figures indicate that with barium sulphate the stomach empties itself twice as fast as with bismuth.

The vehicles employed have been of every sort conceivable, including water, milk, mucilage of acacia, bread and milk, cereal porridges, paps and gruels, mashed potatoes, fermented milk, and mixed meals containing meat. The proportion of opaque salt to suspension medium varies from 10 to 50 per cent. of the former, and the total quantity of the meal given ranges from 6 to 20 ounces or more. Finally, practice differs as to permitting the patient to follow his accustomed habits of eating and drinking during the period of examination. Often this important feature is not mentioned, yet it is known that the taking of food after ingestion of the opaque meal will markedly prolong the evacuation time of the latter.

It is quite apparent that from these differing technics, differing results must follow and this undoubtedly accounts very largely for the varying esteem in which Roentgen tests for motility are held.

The prototype of all the opaque meals now in use was that devised by Rieder,[15] and consisted of 50 gm. of bismuth carbonate in 350 gm. of flour-pap. Rieder considered three to four hours as the normal emptying time for this meal. Commonly half the meal is discharged within an hour. Toward the end of digestion, he remarks, there is a distinct slowing of emptying which he thinks is due to an intestinal reflex. He mentions the experiments of Wulach showing the emptying time of carbohydrate mixtures to be from two and one-half to

14. Groedel, F.: The Influence of Various Contrast Substances on the Motility of the Intestinal Canal, Arch. Roentg. Ray, April, 1913, p. 420.

15. Rieder, H.: Das Roentgen-Verfahren im Dienste der Pathologie und Therapiè des Magen-Darm-Kanales, Verhandl. d. xxix deutsch. Kong. f. inn. Med., J. F. Bergmann, Wiesbaden, 1912, p. 22.

three and one-half hours, albuminous mixtures five or six hours, and fat from seven to eight and one-half hours. The Roentgen method gives a good picture of gastric motility. But, Rieder adds, in spite of the great excellence of the Roentgen motility test, the method formerly used alone of withdrawing a test-breakfast or test-meal will firmly retain its diagnostic worth because it will show in every case not only the motility but also the secretory function.

Barclay[16] has used bismuth carbonate in the proportion of 1 to 2 or 3 of the excipient, for which latter he employs bread and milk, thoroughly mashed up, or porridge. The total quantity given varied from 2 to 12 ounces. With regard to motility he says:

> Retention of bismuth food is the result of pyloric obstruction and Rieder laid it down that the whole of a bismuth meal should have left the stomach within five hours. For diagnostic purposes this is a good enough guide, but I never report definite obstruction unless the delay is well marked. In hospital practice eight hours retention is my standard, but in the vast majority of the cases recorded, some food was still present in the stomach after twenty-four hours. In private practice six hours is my standard, but I always repeat the observation on at least one occasion to verify this finding when the margin of delay is so small.

Groedel[17] at first employed the Rieder carbohydrate meal. An emptying time beyond four hours he regarded as abnormal. Later[18] he began using barium sulphate 250 gm., mixed with 20 gm. each of maize flour, sugar and cocoa in 400 c.c. of water. This meal, he found, emptied normally in two hours.

Kaestle[19] considers two and one-half to three and one-half hours as the normal emptying time of a fluid, carbohydrate (mondamin), contrast meal containing zirconium oxid and weighing 400 gm. A stiff mixture of the same weight may require four hours. Slight delay of evacuation of the fluid meal, up to six hours, he states, may be caused by gastric atony, hyperacidity, reflex pylorospasm, and even beginning pyloric stenosis. Residues after twelve hours or longer occur only with organic pyloric stenosis. Hypermotility may result from a gaping pylorus or strong expulsive energy (hypertonus and hyperperistalsis).

Satterlee and LeWald[20] in their description of the water-trap stomach remarked the occurrence of a residue from the bismuth meal

16. Barclay, A. E.: The Stomach and Esophagus. New York, MacMillan Co., 1913, pp. 9, 36.
17. Groedel, F. M.: Atlas und Grundriss der Roentgendiagnostik. Munich, J. F. Lehmann, 1909, pp. 176, 198.
18. Groedel, F. M.: The Influence of Various Contrast Substances on the Motility of the Intestinal Canal, Arch. Roentg. Ray, 1913, xvii, 420.
19. Kaestle, K.: Lehrbuch der Roentgenkunde (Rieder-Rosenthal). Leipzig, J. A. Barth, 1913, p. 531.
20. Satterlee, G. R. and LeWald, L. T.: One Hundred Cases of Water-Trap Stomach, Jour. Am. Med. Assn., 1913, lxi, 1340.

in many of these cases. "The water-trap stomach," they say, "might almost be considered as a ptosed organ, with the first portion of the duodenum and the pylorus fixed in proper position, giving the characteristic long pyloric arm and resemblance to a water trap." The meal given consisted of 90 gm. of bismuth subcarbonate suspended in 600 c.c. of fermented milk. A residue from this meal, "long after the usual emptying time" was noted in 50 per cent. of the cases. In their conclusions they state: "The typical water-trap stomach of marked degree, which shows a large residue in the stomach after six hours should be operated on when diagnosed."

Cole[21] remarks:

> I have already shown the fallacy of testing the gastric motor efficiency by administering bismuth suspended in fluid or mixed with cereal, and the same is true for intestinal motor efficiency. If the test is to be of value the stomach and intestines must be called on to evacuate such a meal as is normally imposed on them. Therefore, the true test of gastro-intestinal motor efficiency is made by administering bismuth or barium suspended in fluid, preferably buttermilk, in conjunction with a Riegel meal of meat, potatoes and bread. . . . If the stomach is high and of the cow-horn type, especially if a condition of diminished acidity or achylia exists, evacuation will be accomplished very rapidly, perhaps in two hours, whereas many a stomach presenting no organic obstruction requires six hours for complete evacuation.

Baetjer and Friedenwald[22] gave a meal consisting of bismuth subcarbonate, 1½ ounces; in an ordinary glass of water (about 12 oz.) with sufficient mucilage of acacia to make an emulsion. In obstruction from within (pyloric carcinoma, ulcer with cicatrix, idiopathic thickening of the pylorus) they noted gastric retention for from ten to twenty hours. In obstruction from adhesions from chronic appendicitis or after appendectomy, retention for from six to eight hours was found. Gallbladder adhesions showed residue in the stomach after five or six hours. Retention from muscular relaxation (atony) was also observed, but the time factor is not given. They regard from three to four hours as the normal emptying time for a horizontal stomach; from five to six hours for a prolapsed fish-hook stomach.

George and Gerber[23] call attention to the fact that the original Rieder meal contained 40 gm. of bismuth subcarbonate in about 300 c.c. of cooked cereal. Later other mediums and much larger amounts of the opaque salts came into use.

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21. Cole, L. G.: Relation of Lesions of the Small Intestine to Disorders of the Stomach and Cap as Observed Roentgenologically, Am. Jour. Med. Sc., 1914, cxlviii, 92.

22. Baetjer, F. H., and Friedenwald, J.: On the Diagnosis of Incomplete Forms of Pyloric Stenosis by Means of the Roentgen Ray, Boston Med. and Surg. Jour., 1914, clxxi, 261.

23. George, A. W., and Gerber, I.: The Roentgen Diagnosis of Duodenal Ulcer, Surg., Gyn. and Obst., 1914, xix, 395.

As a result of the marked variation of bismuth it is impossible to use the same functional data for diagnosis. . . . This is a point which has not been appreciated by many roentgenologists. They have used various kinds of meals—not only buttermilk, but malted milk, plain milk, water, mashed potato, etc., and have varied the amount of bismuth or barium, and yet have attempted to apply to their work the conclusions based on the observation of functional disturbances in thousands of cases done under the Rieder technic. Obviously this is incorrect. The only proper course left for one who wishes to use these functional data is to accumulate a large number of cases, done with more satisfactory mixtures and check them up with operative results.

In a paper written a few months prior to the above, George and Gerber[24] venture this statement: "The more we have accumulated evidence on this subject, the more we have become convinced that six-hour gastric stasis is the least important factor in Roentgen bismuth diagnosis." Recently they[25] have reiterated this opinion. It should be noted that with their technic the patient is permitted to take food during the six-hour period.

White and George[26] observe that ulcer in some other part of the stomach may cause such spasm of the pylorus that bismuth is retained from two to four times the normal, even up to twenty-four hours, while operation shows the pyloric walls perfectly normal. A considerable residue in the stomach at the end of six hours, with no anatomic defect and nothing found elsewhere to explain it, suggests gastric ulcer, but it is to be remembered that the stomach empties itself entirely in six hours in about one-half the cases of gastric ulcer. These authors state further that the emptying of the stomach depends on several more or less opposing factors, namely, gastric peristalsis, mechanical obstruction at the pylorus or in the duodenum, and the reflex control of the opening and shutting of the pylorus. Ulcer of the duodenum may disturb this reflex, and when acid chyme is squirted into the duodenum the absence of the reflex allows the pylorus to remain open or relaxed, and thus permits rapid emptying of the stomach. They go on to say that when indurated duodenal ulcer or scar tissue or adhesions cause mechanical obstruction, the result depends on the balance of the opposing forces; the stomach emptying in the normal time or earlier or later, according as the obstruction overcomes the tendency to rapid emptying which results from active peristalsis or interference with the pyloric reflex.

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24. George, A. W. and Gerber, I.: The Practical Application of the Roentgen Method to Gastric and Duodenal Diagnosis, Jour. Am. Med. Assn., 1914, lxii, 1071.

25. George, A. W., and Gerber, I.: Observations from the Study of a Thousand Gastrointestinal Cases, Am. Jour. Roentgenol., 1915, ii, 592.

26. White, F. W., and George, A. W.: The Roentgen Ray Method in the Diagnosis of Gastric and Duodenal Ulcer, Boston Med. and Surg. Jour., 1913, clxix, 157.

As a test of motility in those cases in which the stomach tube is contraindicated or refused, Bassler[27] uses a mixed-meal method by which he gives 25 gm. of bismuth subcarbonate with the Riegel meal and examines by the Roentgen ray six hours later, at which time the stomach should be empty. In marked pyloric stenosis he has noted a residue at twelve hours, or much later, even to five days. However, in a subsequent publication, Bassler[28] has this to say:

> In the study of motility and exit from the stomach in 203 cases of distinct gastroptosia, in which hourly Roentgen ray observations were made, the conclusion was plain that the Roentgen ray method of diagnosing stasis in the stomach is not as practical as the test-meal method. One hundred and twenty-six of these cases examined by the bismuth-Roentgen-ray method showed delay of exit of six hours or more, while only thirty-one showed the delay by the test-meal method. . . . Instances were encountered in which bismuth was present in the stomach as late as eighteen hours after ingestion, while the stomach on a mixed meal was empty in four and one-half hours. . . . It is apparent, whatever has been advanced to the contrary, that the method of examination by food extraction is decidedly more to be depended on in gaining an idea of exit from the stomach than is the bismuth Roentgen ray method, for it was strongly suggested that foods pass from the stomach in decidedly less time than will bismuth or any other form of metal salts used to throw a shadow, probably because of the pulverized salts adhering to the mucosa.

The most faithful advocate of the Roentgen motility test is Haudek,[29] and to him we are indebted for the double-meal method of examination, the establishment of the six-hour limit and a vast deal of information concerning the significance of disordered motility as shown by the Roentgen ray. The rather chaotic application of the Roentgen examination for motility led Haudek, in 1909, to establish his double-meal method, partly with the view of saving time and partly to make the test more precise. Accordingly, he began the administration of a Rieder meal in the morning, and examined the patient six hours later, at which time a second Rieder meal was given to complete the examination. The selection by Haudek of six hours as the division line between normal and delayed emptying was explained by him on the ground that while the normal stomach will drive out a Rieder meal in about three hours, as an average, delay to five or six hours might result from physiologic causes. He cited as examples the influence of rest and movement, right and left-side positions, psychic factors, eating or drinking after taking the meal, and sedimentation of the opaque salt.

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27. Bassler: Diseases of the Stomach and Upper Alimentary Tract. Philadelphia, F. A. Davis Company, 1913, p. 213.

28. Bassler, A.: Some Recent Conclusions on Abdominal Roentgen Ray Work, Jour. Am. Med. Assn., 1913, lxi, 2217.

29. Haudek, M.: Die Technik und Bedeutung der Radiologischen Motilitätsprüfung, Verhandl. d. xxix Deutsch. Kong. f. inn. Med., J. F. Bergmann, Wiesbaden, 1912, p. 143.

Even after six hours or longer minute residues might sometimes be found in normal stomachs, and he accordingly ignored mere traces. Small residues, up to a quarter of the meal, he deemed, could be due not only to organic pathologic changes but also to hypomotility from atony, hyperacidity, or long *hubhöhe,* that is, a long, vertical pars pylorica. Larger residues could be almost certainly ascribed to pyloric obstruction by organic stenosis or spasm from ulcer. He also pointed out that the test did not rest alone on the presence or absence of a residue, but that the position of the "head" of the six-hour meal gave gross information as to motility. Normally at or near the cecum, the "head" would be advanced far into the large intestine by hypermotility or held back in the small intestine by hypomotility. Further, on giving the second meal, there could also be taken into consideration the tonus of the stomach, its peristalsis, the freedom of passage through the pylorus, the *hubhöhe,* and thus the total picture would enable an estimation of "the great X of motility, the functioning of the pylorus."

An experience of years with thousands of cases has increased Haudek's confidence in the method. In a recent article, he[30] goes so far as to say that the Roentgen determination of the expelling forces of the stomach gives better results than the older methods, and that it is not only exact and reliable but also very simple. He shows that while the clinical examination cannot determine whether the increase or decrease of motility is due to a change of the expelling power or of the resistance, the Roentgen examination can be much more decisive. While he had previously considered atony to be an occasional cause of six-hour retention he now believes that atony, under otherwise normal conditions, causes only a slight increase of evacuation time, usually below six hours. The most important factor for the evacuation of the stomach is the condition of the pylorus. Lessening of resistance produces the picture of pyloric insufficiency; an increase leads to the highest degrees of stagnation. He enumerates the common causes of increased resistance, both organic and spastic, and cites examples as varied by the functional components of motility. He also mentions Sahli's method of testing the motility with sinking and swimming capsules in differentiating between pylorospasm and organic stenosis, also the effect of papaverin in these conditions. By means of Sahli's capsules the evacuation time of water can be shown; this is usually normal in pylorospasm but prolonged in stenosis. According to Holzknecht the administration of papaverin shortens the emptying time in pylorospasm to normal, increases it in stenosis, and has no effect on a combination of the two.

30. Haudek, M.: Ueber die Radiologische Prüfung der Magenmotilitat und Ihre Resultate, Fortschr. a. d. Geb. d. Roentgenstrahlen, 1914, xxi, 472.

For more than two years past our work has been based on the double meal method of Haudek, and we can unreservedly endorse his claims. For various reasons we have found it advisable to modify his technic in some particulars, but have retained the six-hour limit and adhered rather closely to his general principles. A cereal porridge instead of a pap for the six-hour meal is employed and barium sulphate[31] substituted for bismuth salts. Since barium leaves the stomach earlier than bismuth we believe that a six-hour retention of barium is even more significant than one of bismuth. Until the first of this year patients were required to take castor oil on the evening previous to the day of examination, but this has been abandoned as unnecessary. The observations of Hayes[32] show that purgation results in a heightening of gastro-intestinal motility for a day or two. A comparison of our observations during the past few months with those made previously, indicates that this increase does occur, but that it does not materially affect the six-hour test. Our present routine is as follows:

The patient comes to the laboratory in the morning without breakfast, and usually, but not always, after tubing and lavage by the gastro-enterologist. He is given a meal consisting of 4 ounces of well-cooked wheaten breakfast cereal with 2 ounces of barium sulphate, to which he is permitted to add a little milk and sugar according to his taste. He is instructed to take neither food nor drink, except water, until the examination is finished. Six hours later he returns and the screen examination is begun. The presence or absence of a residue in the stomach from the motor meal is noted. The amount of retention is recorded on a scale of four units, each unit representing approximately a fourth of the meal. If the entire meal has passed into the intestine its position and distribution are observed. The patient is then given 2 ounces of barium sulphate stirred up with 8 ounces of water. Usually some of this escapes or can be driven through the pylorus, showing its condition as to patency. To complete the examination and to fill the stomach for roentgenography, the patient takes about 12 ounces of a potato-starch pap containing approximately 3 ounces of barium sulphate, after which the behavior of the stomach in all respects is watched.

Our gastro-enterologist's routine for examination of the gastric contents is the following: At 6 p. m. previous to the day of examination the patient takes a modified Riegel meal, that is to say, he is instructed to eat an ordinary meal which must include bread, meat

31. As is well known by roentgenologists, only chemically pure barium sulphate is used, other salts of barium being absorbable and toxic.

32. Hayes, M. R. J.: Roentgen Rays in the Diagnosis of Abnormalities of the Intestinal Tract, Clin. Jour., 1914, xliii, 529. Abstr. Surg., Gyn. and Obst., 1915, xx, 138.

and potatoes. An hour later he eats 20 raisins, the skins of which are easy of identification, and tend to remain in the stomach somewhat longer than the usual food materials. The gastro-enterologist's examinations are begun the next day, about 8 a. m., and, depending on the number of patients to be examined, the interval after the motor meal varies from fourteen to sixteen hours. The estimate of motility is based on the presence or absence of food bits or raisin skins from this meal as shown by tubing at the morning examination. Residues are recorded on a scale of 4. The gastro-enterologist's technic also includes the administration of a modified Ewald test-breakfast for the chemical examination, but with this we are not here concerned.

### COMPARISON OF THE RESULTS IN 950 CASES

During the year 1914, 950 patients who had been examined both by the Roentgen ray and the test-meal went to operation. Two hundred and twenty of these, or 23.1 per cent. showed a gastric residue, at the Roentgen-ray examination, from the six-hour meal. One hundred and thirty-one, or 13.7 per cent., had food remnants. In other words, the Roentgen ray showed approximately 70 per cent. more retentions than did the clinical test-meal. The lesions found were: Disease of the appendix, 125 cases; disease of the gallbladder, 311; gastric ulcer, 109; gastric cancer 137; duodenal ulcer 268. The accompanying table shows the incidence of retention in each of these conditions, as shown by the Roentgen ray and stomach tube, respectively. The preponderance of six-hour barium residues over food remnants from the test-meal is noteworthy, being twice as great in gastric ulcer and lesions of the gallbladder; almost twice as great in duodenal ulcer; and half again as large in gastric cancer. In the 125 cases with lesions of the appendix, a retention was noted by the Roentgen ray in only one case, and found in two cases only by the stomach tube. In only 12 of 311 cases with lesions of the gallbladder was retention noted either by the Roentgen ray or by tubing. The vast majority (209 or 90.4 per cent.) of the 220 patients showing a barium retention, were found at operation to have cancer or ulcer of the stomach, or ulcer of the duodenum.

In 16 cases representing all five conditions, the stomach-tube revealed food remnants, while no six-hour retention of barium was found by the Roentgen ray. On the other hand, 105 patients had Roentgen residues but no food remnants.

In eight of the cases tabulated under gastric ulcer there was also duodenal ulcer. All of these patients showed a residue from the barium meal, and six of them had food remnants.

INCIDENCE OF RETENTION OF TEST-MEAL IN 950 CASES

| | Total Number | With Residue (x-Ray) | | With Food Remnants (tube) | | With Residue (x-Ray) only | | With Food Remnants (tube) only | | With Both Residue (x-Ray) and Food Remnants (tube) | | Number Without Residue (x-Ray) or Food Remnants (tube) | No. With Residue (x-Ray) or Food Remnants (tube) or Both |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % | No. | % | No. | % | | |
| Lesions of the appendix..... | 125 | 1 | 0.8 | 2 | 1.6 | 1 | 0.8 | 2 | 1.6 | 0 | 0.0 | 122 | 3 |
| Lesions of the gall bladder..... | 311 | 10 | 3.2 | 5 | 1.6 | 7 | 2.2 | 2 | 0.6 | 3 | 0.9 | 290 | 12 |
| Gastric ulcer ..... | 109 | 50 | 45.8 | 25 | 22.9 | 29 | 26.6 | 4 | 3.5 | 21 | 19.2 | 55 | 54 |
| Gastric cancer ..... | 137 | 83 | 60.5 | 57 | 41.6 | 29 | 21.1 | 3 | 2.1 | 54 | 39.4 | 51 | 86 |
| Duodenal ulcer ..... | 208 | 76 | 28.3 | 42 | 15.6 | 39 | 14.5 | 5 | 1.8 | 37 | 13.8 | 187 | 81 |
| | 950 | 220 | 23.1 | 131 | 13.7 | 105 | 11.0 | 16 | 1.6 | 115 | 12.1 | 714 | 236 |

Besides the cases tabulated above, residues were found by the Roentgen ray in one patient in each of the following conditions: Cancer of the pancreas, tumor of the ileum, cancer of the common duct, hydronephrosis, tumor about head of pancreas, tumor of left kidney, subdiaphragmatic abscess, and cancer of the ascending colon. In the four first mentioned, retention was also noted by the gastro-enterologist.

How can the discrepancy between the gastro-enterologist's results and our own be explained?

First, it would seem probable that the time elapsing between the ingestion of the gastro-enterologist's meal and its withdrawal is too liberal, and that the stomach was empty in many cases, although an actual and pathologic hypomotility existed.

Secondly, it is quite possible that the tube may have failed occasionally to bring up food remnants which were present. Harmer and Dodd,[33] by watching with the Roentgen ray the introduction of the tube, frequently noted that the tip impinged against the gastric wall, well above its most dependent portion, and continued efforts to pass the tube simply caused it to curl and displace the tip further upward. In other instances it was found that by passing the usual length of tube in cases of ptosis, the tip might fail to reach the residuum. This, they believe, is a common error. The posture of the patient and the position the stomach occupies in the abdominal cavity affect the success of tubage. From their observations they regard it as "obvious that failure to recover gastric residuum with the unaided stomach tube from a fasting stomach or after the ingestion of a test-meal cannot be accepted as conclusive evidence of the absence of gastric stasis." Rehfuss, Bergeim and Hawk[34] have employed a tube devised on the principle of the duodenal tube, with a slotted metal tip, which by its weight will seek the most dependent part of the stomach. In instances in which the passage of the ordinary tube failed to disclose any residue, the new tube obtained considerable amounts. They found, further, in a series of healthy persons, that the fluid residuum in the normal empty stomach far exceeded the accepted limit of 20 c.c., and in several was above 100 c.c.

Thirdly, the tube may have failed to reach food retained in the lower loculus of an hour-glass stomach. It seems probable that this occurred in at least one instance of hour-glass stomach where the

33. Harmer, T. W., and Dodd, W. J.: Sources of Error in the Use of the Stomach Tube for Diagnosis: Preliminary Report, THE ARCHIVES INT. MED., 1913, xii, 488.

34. Rehfuss, M. E., Bergeim, O., and Hawk, P. B.: Gastro-Intestinal Studies: The Question of Residuum Found in the Empty Stomach, Jour. Am. Med. Assn., 1914, lxiii, 11.

Roentgen ray showed a residue, but the gastro-enterologist reported none.

Fourthly, marked differences as to the quantity and character of the food taken by the patient may have affected the gastro-enterologist's results.

Fifthly, in exceptional instances of organic stenosis at the pylorus (cancer or ulcer) the tube found retained raisin-skins when the roentgenologic test failed to show a barium retention. It is clear that a stenosis might be sufficiently narrow to block the passage of these skins yet permit a fair exit of finely divided barium.

### APPLICATION OF THE ROENTGEN TEST

It is evident that the double-meal method does not, as a routine, concern itself with hypermotility in terms of exact time of evacuation, although this can be established with either the first or the second meal if desired. As a rule, the degree of hypermotility can be reckoned by the advance of the head of the first meal beyond the cecum, plus the freedom and continuity of exit of the second meal through the pylorus. It is true that the position of the six-hour meal is the net result of the motility both of the stomach and intestine, but in the absence of intestinal obstruction as shown by other Roentgen signs, or severe obstipation or diarrhea as indicated by the anamnesis, the intestinal factor can be disregarded.

In the presence of an evident hypermotility we have to consider as possible causes duodenal ulcer, gastric carcinoma, anacidity and diarrhea. The report of the gastric analysis or the clinical history will decide as to anacidity or diarrhea, respectively. The most typical hypermotility is seen in cancer with its gaping pylorus which may be infiltrated and stiffened or merely relaxed by the anacidity. The flow through the pyloric opening is continuous and frequently voluminous, and the six-hour meal may have advanced into the transverse colon or beyond. The hypermotility of gastric cancer is not incompatible with actual narrowing of the pylorus, which remains steadily open and thus more than compensates for the narrowing. Over 90 per cent. of the gastric cancers will reveal direct Roentgen evidence (filling defects), so that hypermotility is by no means a principal sign. The hypermotility of duodenal ulcer is commonly attributed to interference with the pylorus-closing reflex as well as to hypertonus and hyperperistalsis. Here, again, these factors may balance or even overcompensate a slight organic or spasmodic stenosis at the site of the ulcer. In any event, most of the cases of duodenal ulcer will show hyperperistalsis or other diagnostic signs in the way of an accessory pocket or deformity of the bulb.

An initial rapid rate of clearance of the second barium meal through the pylorus is not alone a dependable sign of hypermotility; the advancement of the six-hour meal in the colon should also be considered. We have seen numerous cases of cholecystitis (with and without periduodenal adhesions) chronic appendicitis, hypochlorhydria from all causes, and general reflex gastrospasm, in which the clearance was large and uninterrupted during five or ten minutes' examination, yet this clearance was probably not characteristic of the whole period of digestion, since the six-hour meal was not advanced beyond its average position.

By the process of elimination few cases of actual hypermotility remain unexplained, and on the whole, it is of less practical importance than its converse.

With the stomach empty at the end of six hours and the head of the motor meal anywhere from the cecum to the hepatic flexure the gastric motility is considered normal, at least so far as the net result is concerned. It does not follow that this finding absolutely excludes any disturbance of either the active or passive factors of motility, since a diminution of one may be offset by an exaggeration of the other. For example, a somewhat stenotic pylorus or duodenum may be balanced by vigorous gastric peristalsis, or an achylia; or a so-called atonic stomach with weak peristalsis may evacuate its contents through an unusually patent pylorus in average time. Hence a stomach that is empty at six hours, with the motor meal at or not far beyond the cecum, is, strictly speaking, normal as to motility only on condition that other elements are normal also, that is, acidity, peristalsis, tonus and pyloric functioning. If any of the latter are definitely abnormal, the presumption is that one abnormality is compensated by some other, and an analysis of the complication may promote diagnostic nicety. With our present limitations, however, a calculation of this sort could easily lead to error by its intricacy. Likewise, between the average emptying time of say three hours and the arbitrary limit of six hours allowed for presumptively normal evacuation, is a rather wide zone for the play of physiologic and occasionally pathologic, factors causing hypomotility. It was precisely to make liberal allowance for these that Haudek drew his line at six hours, and for this reason we have adhered to that line, though our meal probably leaves the stomach earlier than Haudek's. If there is error it is, at all events, on the side of safety. For emptying times greater than three hours but less than six hours, there is a host of possible causes, including depressive psychic states, weak peristalsis, hypotonus or so-called atony, high *hubhöhe,* ptosis, hyperacidity, reflex spasm of the pylorus and slighter grades of stenosis, whether uncompensated or

only partially compensated. In many cases, although the stomach is empty at six hours, retarded evacuation is evinced by the motor meal lying proximal to the cecum, together, sometimes, with scanty initial clearance of the second meal. Often the cause of this moderate hypomotility is manifest in the form, position, peristalsis or tone of the stomach, or the functioning of the pylorus. In our own experience organic stenoses causing delayed gastric evacuation, but within six hours, have been relatively rare. Shortening the time limit to say five hours in order to detect such cases would probably result in greater error by including physiologic and functional delays.

The six-hour limit allows for delay resulting mainly from weakened active factors of motility—tonus and peristalsis. Delay beyond six hours signifies, as a rule, some disturbance of the passive factor, namely, organic or spastic obstruction at or near the pylorus. It should be reiterated that this delay must be shown by a substantial and visible residue, not mere traces held in the gastric folds, nor a collection in the lower pole so small that it can be seen only with difficulty. With a retention of one-fourth or more of the meal, either obstruction of an organic character probably exists or a serious lesion interfering reflexly with emptying. Among the causes of organic obstruction we have noted duodenal and pyloric ulcer with cicatricial contraction, hypertrophic pyloric stenosis, pedunculated benign tumors (polyposis) pyloric carcinoma, syphilis of the stomach, carcinoma of the upper jejunum, and adhesion bands from inflammatory processes in the right upper abdominal quadrant, usually pericholecystitis. Other causes of obstruction mentioned in the literature are foreign bodies (hair-balls, fruit-stones, etc.), kinking of the prolapsed stomach at its duodenal anchorage, adhesions from chronic appendicitis, and tumors outside the duodenum pressing on it, although we have not encountered a six-hour retention attributable to any of these, except possibly the last.

Small residues down to an eighth or less of the motor meal may, of course, also result from organic narrowing. A more common cause is spasm of the pylorus occurring reflexly from a lesion of the stomach itself, such as ulcer, or from an extrinsic pathologic focus, most often the gallbladder or appendix, and also, but rarely, from more remote abdominal lesions. Holzknecht[35] has remarked the possibility of a six-hour bismuth residue from pyloric spasm due to morphinism, or a single administration of morphin at the time of examination.

In explaining the mechanism by which gastric retentions are produced in the absence of an organic stenosis, roentgenologists have frequently assigned "pylorospasm" as a cause. Now, by the clinician,

35. Holzknecht, G.: The Roentgen Diagnosis of the Stomach, Arch. Roentg. Ray, 1911, xv, 206.

the term is limited to a spasmodic contraction of the pylorus accompanied by pain, vomiting, etc., occurring commonly as a symptom of extragastric conditions, for example, disease of the gallbladder. Roentgenologically, the word has been used rather broadly, perhaps somewhat loosely, to cover an irritable, or hypertonic, or spastic pylorus, which relaxes less freely or less frequently than the normal pylorus, regardless of symptoms. Thus Lippmann[36] takes J. T. Case to task concerning the matter, and goes on to say:

> Roentgenologists habitually diagnose pylorospasm when they find a six-hour residue in a highly acid stomach showing clinically no signs of pylorostenosis. They know, however, that it cannot be true. Firstly, in the great majority of cases they can press this bismuth through the pylorus into the duodenum by effleurage with the hand or with the distinctor of Holzknecht. Secondly, a jet of bismuth water will often dash through the pylorus into the duodenum although the residue remains. Most important of all, I have often passed the large Gross duodenal tube through the pylorus without any difficulty. I have even passed the tube while the six-hour residue was in the stomach in a few cases. Certainly a pylorus which allows a large lead ball to pass is not inclined to pylorospasm. It seems to me that the residue is due to the sinking of the bismuth in the excessive fluid secretion which is so often associated with gastric and duodenal ulcer cases. Most of the men believe that the residue is due to pylorospasm plus hypersecretion, but in consideration of the facts mentioned above, I believe that pylorospasm in its purely clinical sense is a negligible factor in the ordinary case with a six-hour residue.

As a matter of fact, a pylorus which is not organically stenosed is not infrequently seen to remain closed continuously or for abnormally long periods during the Roentgen-ray examination of anatomically normal stomachs showing a six-hour retention, and whether the term "pylorospasm" be strictly applicable or not, the condition cannot be ignored as a probable cause of gastric retention.

As remarked previously, Haudek has mentioned the high *hubhöhe*, that is a long, steeply ascending pyloric arm, as a cause of hypomotility. Of very similar character is the "water-trap stomach" of Satterlee and LeWald, in many cases of which, with their technic, six-hour residues were noted. In both these conditions there is usually a degree of gastric atony. Cannon[37] holds that, in the normal stomach, drainage by gravity is an unfortunate conception, that the food is in exact equilibrium and that muscular action is necessary to its progression. Haudek claims, on the other hand, that the existence of an impeding action of a high level of the outlet has been shown experimentally, as there is a shortened evacuation time in the right lateral position and a prolonged evacuation time in the left lateral position.

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36. Lippmann, C. W.: Pylorospasm, Jour. Am. Med. Assn., 1914, lxii, 2031.
37. Cannon, W. B.: The Mechanical Factors of Digestion. New York, Longmans, Green & Co., 1913, p. 47.

Neilson and Lipsitz[38] have found from experiments on healthy young men that lying on the right side produces a more rapid evacuation of water than does any other position, and that lying on the back causes a quicker emptying than the upright posture. In the light of these statements it would appear that while gravity probably plays a minor rôle in gastric evacuation, as compared with other factors, it cannot be altogether disregarded. Whether a high situation of the pyloric outlet, without an associated gastric atony, may or may not cause a delay of evacuation, we have not noted such delay go beyond six hours with the barium meal. Nor have we noted a six-hour residue attributable simply to hyperacidity, atony, or intestinal stasis with or without "kinking of the duodenum." While the motility of the stomach in a given case is susceptible of some variation from time to time, we have seldom seen a six-hour retention which did not recur at a subsequent examination. But, in the case of a residue without any other diagnostic indications, the test with the motor meal should be repeated before drawing conclusions. On the whole it would seem that Holzknecht[39] was not speaking extravagantly when he said: "Haudek's method of the double bismuth meal has at one step promoted the motility test to the first place in the Roentgen examination of the stomach."

The interpretation of the results from the double-meal method may be either simple or complex as desired. The observer may be content with determining the presence or absence of a residue at the end of six hours. With the presence of such a residue he can be fairly certain of organic pathology somewhere in the gastro-intestinal tract, and probably in the stomach or duodenum. Again, he may also take cognizance of hypermotility or lesser degrees of hypomotility. Still again he may consider the results in the light of all the discoverable factors pertaining to motility, including the gastric form, position, tonus, peristalsis, and acidity. Finally, he may combine and correlate his findings with other roentgenologic signs, the physical examination and the clinical history. By the construction of "symptom-complexes" in this manner Holzknecht[39] was enabled to make diagnoses which otherwise could not be made, and we have routinely followed this plan to advantage. While this has been criticized as an "indirect" method in comparison with the "direct" method, namely that of proving the presence of a lesion by showing local deformity of contour, we can only say that we have often failed to discover such deformity although

38. Neilson, C. H., and Lipsitz, S. T.: The Effect of Various Procedures on the Passage of Liquids from the Stomach, Jour. Am. Med. Assn., 1915, lxiv, 1052.

39. Holzknecht, G.: The Roentgen Diagnosis of the Stomach, Arch. Roentg. Ray, 1911, xv, 206.

the symptom and sign-complex established the diagnosis. Certainly deformity of contour is of the highest roentgenologic value and should be zealously sought for, but, like all other signs it fades gradually into the realm of uncertainty. A six-hour residue is a strong stimulus to careful search for direct signs, and, if the latter are found, the presence of a retention is added assurance that the eye is not deceived, that a lesion exists and that it is interfering with motility, which latter information is important to the surgeon. A diagnosis which takes into account all the facts obtainable from all sources is less likely to go astray than one which rests on a single phenomenon.

Gastric retention can be combined into various indicative complexes. A six-hour residue with a stomach of normal contour, showing hyperperistalsis, means obstructive duodenal ulcer more than ninety times out of a hundred. Residue plus an apparently normal gastric outline, plus an irregular, vigorous peristalsis, chiefly on the greater curvature, usually signifies a lesion involving the pylorus. A residue with an achylia, but without gross alteration of the gastric contour, should suggest the probability either of a small obstructing pyloric carcinoma, or obstruction of the duodenum by pericholecystic adhesions; careful attention to the pyloric and duodenal contours will usually make the distinction. Residue with hyperacidity and no irregularity of the gastric or duodenal outline would indicate a stomach reflexly affected by some other abdominal condition, notably cholecystitis or appendicitis. Innumerable but practicable complexes can be formulated by the introduction of other related data. We have on other occasions emphasized the importance of a general correlation in every case.

The possibilities of the roentgenologic estimation of motility are by no means exhausted. The method described in detail deals with the evacuation of a carbohydrate meal only. We can freely endorse its convenience and trustworthiness in the diagnosis of the graver and usually surgical conditions. By a mixed meal and an extension of the time limit, or by examination at short intervals, or by testing the motility of each individual for carbohydrates, proteins and fats separately, the diagnosis of slighter disturbances of motility, amenable to medical treatment, might be assisted. But, with all the work of the experimental physiologists before us, no meal can be devised the normal emptying time of which can be foretold with certainty, and any test must be proved by trial with an abundant material.

As a caricature may sometimes serve to show the truth better than a photograph, so a diagrammatic representation of motility may assist a clearer understanding. Taking as a basis a meal which leaves the normal stomach in an average time of say three hours, such as

the bariumized carbohydrate meal, we may divide gastric evacuation time as represented on a scale of hours into three zones, viz.:

1. A zone of normal motility
2. A zone of pathologic hypermotility.
3. A zone of pathologic hypomotility.

1. The zone of normal motility must extend from an emptying time somewhat less than three hours to an emptying time somewhat greater than three hours, since we can only fix the three-hour point as an average, on either side of which a variation may be due to purely physiologic causes. Within this zone we are also obliged, as a conservative measure, to include slighter tendencies to hypermotility or hypomotility from causes which, though pathologic, are not pronounced or are compensated wholly or in part. General knowledge justifies the assumption that such variation toward hypermotility is not wide, and, for the purpose of this diagram, we may choose the two-hour point as the normal minimum. The variation toward hypomotility we may grant to be much wider; Haudek makes a generous allowance to the end of the sixth hour which we will accept. The contents of this normal zone would then include:

(*a*) Normal motility. (Example: A normal stomach functionating in a normal manner.)

(*b*) Early emptying, physiologic. (Example: A hypertonic, steerhorn stomach.)

(*c*) Early emptying, pathologic, but partially compensated. (Example: Duodenal ulcer with obstruction sufficient to prolong the evacuation time to two hours in spite of an associated hyperperistalsis, hypertonus and free pyloric patency.)

(*d*) Disordered motility with abnormal but balanced factors. (Example: Stenosing carcinoma with achylia, yet with a net emptying time of three hours.)

(*e*) Delayed emptying, physiologic. (Example: A somewhat hypotonic fish-hook stomach.)

(*f*) Delayed emptying, pathologic, but partially compensated. (Example: Stenosis with hyperperistalsis, emptying being retarded, but within six hours.)

2. The zone of hypermotility, restricted to an emptying time less than two hours, would include such frankly pathologic conditions as nonobstructing gastric carcinoma, duodenal ulcer and diarrheic conditions.

3. The zone of hypomotility, beyond six hours, would comprise the stenoses, both organic and spasmodic, as examples of which may be mentioned obstructing pyloric carcinoma or ulcer, markedly obstruct-

ing duodenal ulcer, and reflex pylorospasm from disease of the gall-bladder, or gastric ulcer remote from the pylorus.

As a matter of fact we know that these zones may overlap each other and that time alone will not delimit normal from abnormal motility. The diagram, while somewhat practical in a way, illustrates the time factor only, and, as said before, a final opinion must rest on an analysis of all the factors. By the Roentgen method this analysis is both possible and practicable, and herein lies its superiority to the test-meal and tube.

| | Hours | |
|---|---|---|
| Zone of Hypermotility... | 0 | |
| | 1 | Early emptying, pathologic. (Nonobstructing gastric carcinoma. Duodenal ulcer. Diarrheic conditions.) |
| Zone of Normal Motility | 2 | Normal emptying. (A normal stomach functionating in a normal manner.)<br>Early emptying, physiologic. (Hypertonic, steer-horn stomach.) |
| | 3 | Early emptying, pathologic, but slight, or partially compensated. (Duodenal irritation. Duodenal ulcer with obstruction sufficient to prolong the evacuation time to two hours in spite of associated hyperperistalsis, hypertonus and free pyloric patency.) |
| | 4 | Disordered motility with abnormal but balanced factors. (Stenosing carcinoma with achylia; average emptying time.)<br>Delayed emptying, physiologic. (Hypotonic |
| | 5 | fish-hook stomach.)<br>Delayed emptying, pathologic, but slight or partially compensated. (Slight stenosis. Stenosis with hyperperistalsis; evacuation retarded but within six hours.) |
| | 6 | |
| Zone of Hypomotility.... | 7 | Delayed emptying, pathologic.<br>Stenosis.<br>(*a*) Organic. (Obstructing pyloric carcinoma. Pyloric ulcer. Obstructing duodenal ulcer. Periduodenal adhesions, etc.)<br>(*b*) Spasmodic. (Reflex pylorospasm from ulcer on the lesser curvature, cholecystitis, appendicitis, and remote abdominal lesions.) |
| | 8 | |
| | Etc. | |

## CONCLUSIONS

1. It would seem that the bariumized carbohydrate meal described above is a more sensitive test for gastric motility than the modified Riegel meal as commonly used in the Mayo clinic.

2. The roentgenologic double-meal method is more informative than tubing after a motor test-meal, since the former not only shows delay of evacuation beyond six hours, but also yields information as to hypermotile conditions, and often by showing both the active and

passive factors concerned in motility, aids in the judgment of the net result.

3. A distinct residue after six hours from the barium meal given under the conditions prescribed has been, nine times out of ten, in our experience, indicative of grave pathology and usually denotes obstruction at or near the pylorus.

4. The roentgenologic method is probably capable of further elaboration and refinement. By this means the motility of the stomach for various food-stuffs, given separately and in combination, can be determined with ease and accuracy and by such determinations the diagnosis of gastric disorders might be further promoted.

5. The six-hour barium residue may be the most definite and striking roentgenologic sign of a gastro-intestinal lesion. Other signs may be so slight and indefinite that a diagnosis might not be ventured without this retention.

6. Retention of the barium meal is often an important element in roentgenologic symptom-complexes as used in diagnosis. In the absence of other decisive roentgen manifestations this finding may have considerable value in correlation with the clinical data.

# UROBILIN IN THE STOOL IN PERNICIOUS ANEMIA AS INFLUENCED BY SPLENECTOMY, TRANSFUSION AND SALVARSAN *

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On account of the peculiar course of pernicious anemia, characterized as it is by marked remissions, there has always been great difficulty in judging fairly the effect of any method treatment. Brilliant results have been reported in certain cases from almost every therapeutic measure employed, yet it is impossible to say in many of these cases that a spontaneous remission was not beginning at the time of treatment, since the blood picture often fails to give this information. It is therefore desirable that a more reliable method be employed for determining the different stages in the course of the disease.

Since this form of anemia is accompanied by a greatly increased blood destruction, it seems not unreasonable to assume that the quantity of blood being destroyed may be regarded as an indication of the severity of the disease process. This can be determined by estimating the quantity of urobilin in the stool, since it has been shown that the amount of urobilin excreted depends directly on the degree of blood destruction present. In a previous study[1] of the variations in urobilin excretion in a variety of conditions, including both primary and secondary anemia, malaria, jaundice from various causes, cirrhosis, etc., it was found that only those cases which gave evidence of increased blood destruction clinically, showed an abnormal urobilin output. There were eleven cases of pernicious anemia, all of which had an increased urobilin excretion, while on the other hand six cases of secondary anemia all showed a urobilin output within normal limits.

Determinations were made on nine cases of pernicious anemia with the hope of being able to demonstrate some definite effect of treatment on the urobilin output. The estimations were begun in every case before treatment and continued during periods of time lasting from two weeks to three months. Following the different forms of treatment, averages of the estimations were made over weekly intervals

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* From the Medical Wards of the Massachusetts General Hospital.

1. Robertson, O. H.: Urobilin in the Stool—An Index to Blood Destruction, THE ARCHIVES INT. MED., 1915, xv, 1072.

when possible, as this period of time seemed a fair measure of the effect produced. The method used was that described by Wilbur and Addis,[2] which consists in extracting the urobilin from the total twenty-four-hourly stool with acid alcohol. This extract is then diluted till the characteristic spectroscopic absorption bands of urobilin disappear and the reading made at this point. Estimations in normal persons average about 5,000 dilutions of the original volume of the stool.

In six of the cases, splenectomy was performed, three received salvarsan, and four were transfused. Of the four cases transfused, one had previously been given salvarsan. The other three were cases of splenectomy who were transfused before operation.

### SPLENECTOMY

There are a few cases of pernicious anemia reported in the literature in which quantitative urobilin estimations were made before and after operation. Eppinger and Ranzi[3] report the most successful series and in their five patients there was a drop to normal in every instance following splenectomy. In one case the urobilin was still low after seven months. They do not say whether estimations were made later in the other four cases or not. All five showed marked improvement. Huber's[4] patient still had a high urobilin output five weeks after operation. It was quite evident, however, that blood destruction was still going on, since the red cells showed a marked decrease in number during the ten days following the estimation. Moffitt[5] reports one case in which the urobilin was still increased one week after operation, but estimations could not be continued as the patient died shortly afterwards from a complicating infection.

McCrudden[6] found in one case, three weeks after splenectomy, a urobilin output twice as great as it had been before. At the time the estimations were made, however, the red count was falling rapidly. Four months later the patient had shown considerable improvement, the red count was increasing, and the urobilin was found to be normal. A second case showed no benefit from splenectomy and although the urobilin decreased from its high figure given before operation, it did not reach normal.

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2. Wilbur, R. L., and Addis T.: THE ARCHIVES INT. MED., 1914, xiii, 235.
3. Eppinger, H., and Ranzi, E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1914, xxvii, 796.
4. Huber, O. R. C.: Berl. klin. Wchnschr., 1913, l, 2179.
5. Moffitt, H. C.: Am. Jour. Med. Sc., 1914, cxlviii, 817.
6. These two unreported cases are cited with the kind permission of Dr. Francis McCrudden of the Robert Brigham Hospital, Boston.

In the six cases of this series treated by splenectomy,[7] the urobilin estimation before operation varied from 10,300 to 46,000; the highest was given by Patient 3, who showed the most rapid drop in red count and hemoglobin. Immediately following splenectomy there was a marked diminution in urobilin output which reached normal in all but two cases.

In Case 1 it is seen that the urobilin output three and one-half months after splenectomy was not only normal, but exactly the same as it was immediately afterwards. During this time the number of red cells had increased from 2,500,000 to 5,000,000.

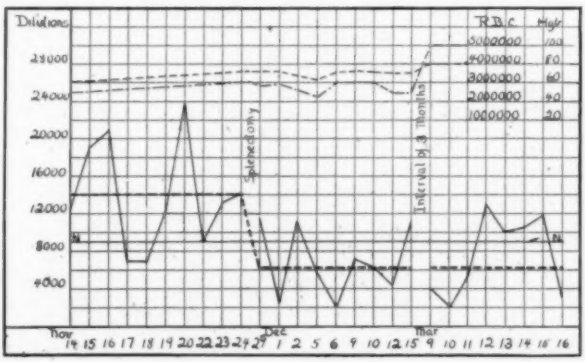


Chart 1 (Case 1).—The curves in this and Charts 2 and 3 have the following significance: ————, daily urobilin excretion; — — — —, average daily excretion; ————, upper limit of normal average daily excretion; — — — —, hemoglobin; — - — -, red blood cells. N. B.—The normal average daily excretion is about 5,000 dilutions.

The urobilin in Case 2 immediately before splenectomy was not as much above normal as in the other cases, yet the drop afterwards was quite as definite. At the end of three months, however, the patient showed an output of 14,000. While there was definite improvement both in his general condition and blood, yet the blood picture still showed the characteristic appearance of pernicious anemia and the red cells were slightly under 4,000,000.

Case 3 just before operation gave the exceedingly high estimation of 46,000. There was an immediate drop to 14,600 afterwards, with a subsequent rise to 20,000 at the time of discharge from the hospital. During this time he had shown a striking improvement generally and

7. A complete clinical report of Cases 1 to 5 appears in The Journal of the American Medical Association, 1915, lxv, 216.

his red cells had reached 4,000,000, but the appearance of the cells was unmistakably that given by pernicious anemia.

The chart of Case 4 was almost identical with that of Case 1, except that before operation the urobilin was 13,000 and the red count 1,500,000. Immediately following splenectomy the urobilin dropped to 3,500 and two and a half months later was 7,400. The qualitative and quantitative improvement in the blood was equally as marked as in Case 1.

Case 5 had a red count of about 2,000,000 and a urobilin output of 14,000. Following operation the urobilin dropped at once to 7,900. After two months and a half it had increased to 16,000 which was higher than before operation. He had shown the least improvement of any of the patients and at the time the last estimations were made his red cells numbered only 2,900,000.

Case 6 before splenectomy had a urobilin output of 21,900 and a red count of 1,632,000. This patient showed the same evidence of marked bone marrow stimulation following splenectomy as seen in the other five cases, i. e., the appearance of blasts and Howell-Jolly bodies in the blood. The urobilin dropped to 16,900 but did not go any lower while under observation. The number of red cells at the time of discharge was practically the same as before operation, but there was definite improvement in the general condition. No further estimations have been made, since this patient was the last one of the series operated on and has only just left the hospital.

The marked drop of urobilin in these cases is of considerable significance, since it completes the picture of a beginning remission. The appearance in the blood of blasts and Howell-Jolly bodies indicated bone marrow stimulation, while the decrease in urobilin output indicated an accompanying diminished blood destruction. The return to an increased output in Cases 2 and 5 is in accord with the persistent markedly abnormal appearance of the blood picture. The same may be said of Cases 3 and 6, which showed a definite drop but did not return to normal.

### TRANSFUSION

The influence of transfusion on urobilin excretion seems to depend chiefly on the reaction of the patient to the newly introduced blood. Three of the four cases showed a definite stimulation of the bone marrow and in all three the urobilin output was temporarily increased. The fourth showed no such change.

Case 2 showed the most marked stimulating effect of transfusion. The red cells increased from 1,600,000 immediately afterwards to 3,200,000 within six days and there was an accompanying shower of blasts. At the same time the urobilin increased from 17,000 to 22,000

This case shows quite strikingly how the urobilin output follows the changes in the course of the disease, the beginning remission being accompanied by a drop to normal.

Cases 3 and 6 were also transfused. In Case 3 the resulting numerical increase was not marked, but the appearance of blasts made it seem certain that bone marrow stimulation had occurred. The urobilin before transfusion was 30,000; during the week following it was 46,000. At this point splenectomy was done, so it was not possible to observe the effect further. Case 6 showed during the week preceding transfusion, a urobilin excretion of 20,900. During the week

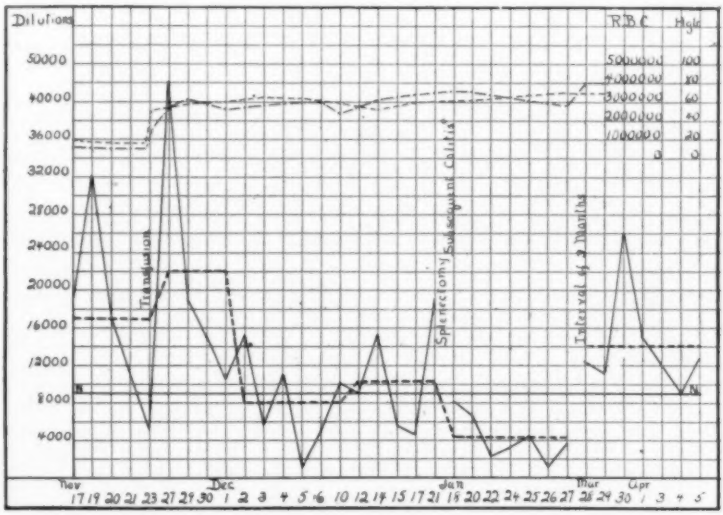


Chart 2 (Case 2).—No tests were made during period of colitis as estimations on diarrhea stools are inaccurate. This is due to the fact that with an increased rate of passage of the bile through the intestinal tract, a smaller proportion of bile than normal is transformed into urobolin.

following, it had increased to 30,000 and at the same time the red cells increased from 1,400,000 immediately after transfusion, to 2,300,000. The patient then had a severe attack of tonsillitis which seemed to check the beginning remission as the blood count ceased to rise and even showed a downward tendency. The urobilin returned to its former level.

Case 7 had received previously several doses of salvarsan. Following transfusion there was no change in the blood other than the temporary increase in the number of red cells due to the newly introduced blood. From the chart one might infer that instead of increasing,

as in the other two cases, the urobilin output was diminished after transfusion. However, on account of the fact that two weeks had elapsed since the last estimation, one cannot say whether the drop occurred before or after transfusion. At any rate it seems quite apparent that there was no increase in urobilin.

### SALVARSAN

The administration of salvarsan seems to have no constant effect on urobilin secretion. Case 7, as indicated in the chart, received five injections of salvarsan at weekly intervals. Three of the doses were followed (Chart 3, Case 7) by a drop in urobilin and two by a decided

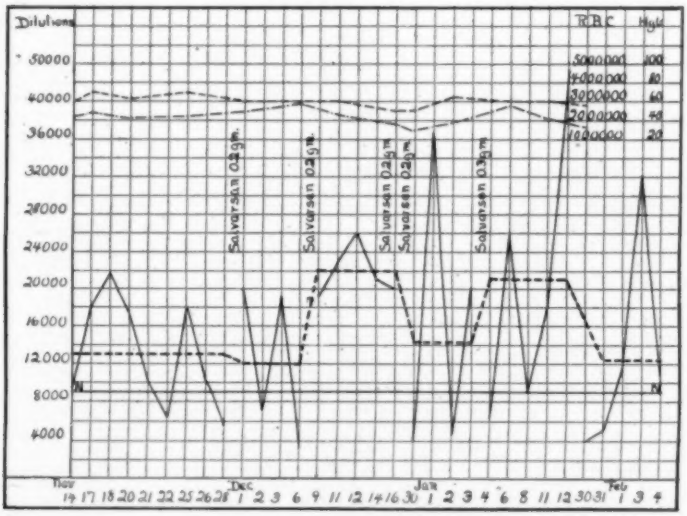


Chart 3 (Case 7).—Urobilin curves during the administration of salvarsan.

rise. But it will be noted that accompanying these fluctuations in the urobilin, there were corresponding variations in the red count. When the number of red cells was diminishing there was an increase in the amount of urobilin excreted, denoting a greater blood destruction; while on the other hand, when the red cells began to increase there was an immediate decrease in urobilin, indicating a lessened degree of blood destruction. Since the blood count showed no constant change following salvarsan, we seem justified in concluding that this drug had very little, if any, effect on the urobilin excretion in this case.

Case 8 had an output of 30,000 before salvarsan. During the two weeks following a single dose—0.3 gm.—the urobilin dropped to

12,500. This showed undoubtedly a marked decrease in blood destruction. However, a complicating factor entered here in the form of a severe throat infection which began about this time, and produced marked prostration. The patient died at the end of two weeks. A plausible explanation of the decreased urobilin output in this case was a diminished blood production, due to bone marrow injury resulting from extreme toxemia, rather than to any effect of salvarsan.

Case 9 received two doses of salvarsan. Following the first dose there was no change in the urobilin excretion. Estimations could not be made after the second as the patient became incontinent of feces.

This absence of any real effect of salvarsan on the urobilin output coincides with the absence of symptomatic improvement in these patients.

## DISCUSSION

From a study of these nine cases it is seen that the effect of treatment on the urobilin is most marked in the cases of splenectomy. Here the drop in urobilin output, occurring long before there was any change in the number of red cells, gave us early information as to the benefit resulting from this procedure. Again, the finding of a high urobilin excretion in several of the cases months after splenectomy, together with the abnormal appearance of the red cells, makes it seem doubly certain that the improvement in these cases is only temporary, in spite of the fact that the number of red cells is well up toward normal.

Judging by the variety of both clinical and blood pictures seen in grave anemia, it seems reasonable to assume that the bone marrow may show varying degrees of functional activity. This may range on the one hand from a markedly hyperactive bone marrow, associated with a great increase in blood destruction, to a very much depressed bone marrow activity on the other, presumably resulting from extensive injury, and unaccompanied by abnormal blood destruction. Splenectomy has been advocated in pernicious anemia on the theory that by taking out the spleen, the chief hemolytic agent is removed. Therefore this operation should have its most marked beneficial effect in those cases in which the anemia is accompanied by a greatly increased blood destruction. Thus, in deciding the advisability of splenectomy it seems fair to regard the urobilin output as one of the important indications of how much benefit may be expected from this procedure. But when the anemia results chiefly from a depressed marrow functioning, we would expect much less benefit from splenectomy, or none at all, depending on the degree of bone marrow injury. This latter type in its most marked form—aplastic anemia—is a rare condition.

## SUMMARY AND CONCLUSIONS

1. Splenectomy: In six cases of pernicious anemia with splenectomy, the urobilin output which had previously been high, showed a marked decrease immediately after operation. The two cases in which the urobilin later returned to a high figure, as well as one case with a persistently increased output, showed definitely less improvement than the two cases in which the urobilin remained normal.

2. Transfusion: Three of the four patients transfused gave evidence of a resulting bone marrow stimulation and at the same time showed a temporary increase in urobilin excretion. The one case in which transfusion was without effect showed no such increase.

3. Salvarsan: In three patients treated with salvarsan, there was practically no effect, either on the course of the disease or on the urobilin excretion.

4. It seems fair to conclude that:

1. Variations in the urobilin output may be taken as an index of corresponding changes in the course of the disease.

2. Such variations in the urobilin may occur before there is any change in the number of red cells.

3. The determination of the urobilin output as an index of blood destruction is the most accurate means we have of estimating the effect of treatment.

Massachusetts General Hospital.

# METABOLISM STUDIES BEFORE AND AFTER SPLENECTOMY IN CONGENITAL HEMOLYTIC ICTERUS *

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In this communication we present the results of a study of the metabolism, before and after splenectomy, in a child 5 years of age suffering from congenital hemolytic icterus with splenomegaly. As Dr. S. McC. Hamill, to whom we are indebted for the opportunity of making these studies, will, in a later communication, offer a consideration of the clinical and therapeutic problems involved, we will, aside from the metabolic studies, present only a brief abstract of the clinical history, a note on the pathology of the removed spleen and a table (Table 1) of the blood examinations before and after operation.

## ABSTRACT OF CLINICAL HISTORY

At birth, at term, the child weighed 7 pounds and is described as lacking the characteristic red color of the newly born. About twenty-four hours after birth the "alabaster whiteness" of the skin, which the mother describes, changed to a mahogany brown which lasted three months, gradually fading to a sallow pallor, which has persisted. At six months, when the child passed through an attack of pneumonia, it weighed only 10 pounds. The general health was poor and gastro-intestinal disturbances frequent. In the fourteenth month the first severe anemia, accompanied by dark brown discolorations of the skin and preceded by protracted vomiting and diarrhea, was observed. Two months later a similar attack occurred with the new feature of marked edema of the entire body. During these attacks the rectal temperature usually rose to 104 or 105. Periods of recrudescence and exacerbation followed one another until the child was 2½ years old when an unusually severe attack kept him in bed for five months. Vomiting and diarrhea were severe and hemorrhages from the nose and bowel were frequent and difficult to control. During the second month of this period a partial paralysis of the left side developed. At this time an injection of neosalvarsan was given, more for the hematinic action of the arsenic, than with any suspicion of lues. Gradual improvement

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* From the John Herr Musser Department of Research Medicine, University of Pennsylvania.

followed this treatment and after the paralysis had disappeared, except for a residual spastic palsy of the left leg, the child enjoyed fairly good health. The Wassermann reaction frequently repeated has always been negative. During the eight months following this attack, salvarsan was given five times by rectum. About the time he was 5 years old and again seven months later, he lost the power of speech, was more or less delirious and complained of pain in his head. At 3½ and again at 4½ years, he had an otitis media. His appetite has always been poor, never normal, and at times he refused to eat. A tendency to localized edema, especially of the face and of the hand, has been constantly noted. He tires easily and frequently complains of this. Obstinate constipation has been the rule and the feces are described as dark or orange in color.

From the family history, it is found that a sister was jaundiced for ten days and a brother for two days after birth, but these children, now 15 and 13 years of age respectively, have otherwise been in good health. The father is said to have had an enlarged spleen and offers a history of exposure to lues, of skin eruption and chronic abscess of joint and ankle. The mother, three months before the birth of the subject of the present study, was paralyzed and suffered a separation of the pelvic bones. The delivery was under anesthesia.

*Laboratory Examinations.*—An examination of the numerous clinical records which have accumulated shows that the urine offers nothing of unusual interest. The only positive finding is an occasional slight trace of albumin. Tests for bile have always been negative and urobilin tests have shown no increase of this substance. Examinations of the feces indicate that food is well digested; tests for occult blood have been negative and no parasites or ova have been found. No records of the early blood examinations have been preserved, except a brief record that at the time of the first severe attack (when fourteen months old) the hemoglobin fell to 24 per cent. and a diagnosis of pernicious anemia was made. A number of counts made during the years 1913 and 1914 showed considerable variation in both hemoglobin (from 65 per cent. to 28 per cent.) and red blood cells (4,180,000 to 1,360,000). The Brulé test and tests for cross hemolysis with normal serum and cells were negative. (These were performed by Dr. E. B. Krumbhaar.) The subsequent blood counts are summarized in Table 1.

At the beginning (Dec. 3, 1914) of our metabolism studies one of us (O. H. P. P.) made a complete examination of the child, and from the notes at that time, the following abstract of positive nndings has been prepared:

The boy is 5½ years of age, 105.5 cm. in height, weighs 39 pounds, is well nourished and of good muscular development. His skin is slightly sallow, but there is no true jaundice. Over the vessels of the neck, a systolic bruit is

heard and an occasional slight systolic whiff is heard at the apex of the heart. At the base of the heart, the first sound is replaced by a systolic murmur of a blowing character and the second sounds are accentuated. Normal sounds are heard at the tricuspid area. The liver is doubtfully palpable. The splenic dulness begins in the midaxillary line at the sixth rib and extends down a little below the line of the umbilicus; its greatest length is 18 cm. and its greatest width about 9 cm. The spleen feels firm, smooth and without distinct notches.

The right lower extremity is normal; the left lower extremity normal as to thigh and leg, but the ankle and foot show a spastic paralysis. The urine at this time was amber in color with no gross sediment; the specific gravity was 1.029; tests for albumin, sugar, acetone, diacetic acid, indican and bilirubin were negative. The test for urobilin gave a doubtful reaction; under the microscope some mucus was seen but no cells, casts or crystals. The blood count at this time is given in Table 1, under the date of Dec. 3, 1914.

The first metabolic period ran from the fourth to the fourteenth of December and during this time there was little or no change in the patient's condition. Throughout the period there was a tendency to elevation of temperature which, however, rose but once over 101. The child was not kept in bed, ate regularly and required no medication or cathartic. At the end of the period, he was discharged to return after Christmas.

During the interval at home (Dec. 14, 1914, to Jan. 26, 1915), no noteworthy change in condition occurred. On January 26, the patient was readmitted to the University Hospital, service of Dr. Charles H. Frazier. Physical examination revealed nothing new; examination of the blood and urine showed but little change. On January 28, the spleen was removed by Dr. Frazier, under ether anesthesia. The operation was uneventful and there was only a trifling loss of blood. At the time of the operation the coagulation time of the blood was found to be about four minutes and tests for resistance of red cells showed beginning of hemolysis in 0.65 per cent., and complete hemolysis in 0.425 per cent. salt solution. Convalescence after the operation was satisfactory and on February 4, the patient was transferred to the medical service, and the second period of metabolism study was started on February 5. At this time the child's weight was 40 pounds.

On the fourth day of metabolism study, an attack of bronchitis caused a rise of temperature to 103 and for two or three days there was some loss of appetite, and on the ninth day, a mild otitis media developed. Despite these disturbances, the metabolism study was continued until the period of ten days representing the eighth to eighteenth days after splenectomy was completed.

At the end of the period, the child's weight was 38½ pounds and he seemed considerably improved in color and strength. The appetite was good. The condition of the bowels demanded an occasional cathartic which, however, never caused watery stools. Even before discharge on February 18, just three weeks after operation, it was

evident that a marked improvement in the blood picture had occurred, both hemoglobin and red blood cell count being double that obtained on the first admission.

After discharge, the improvement continued steadily with greatly increased appetite and strength. The skin lost its sallow hue and became normal in appearance. In the two months since operation the child has enjoyed uninterrupted good health except for one attack of indigestion, the result of overfeeding. Two weeks previous to the last blood count given in the table a rather severe nasal hemorrhage occurred as a result of excoriations. The lowered hemoglobin in the last count is probably to be explained by this hemorrhage.

### PATHOLOGIC DESCRIPTION OF THE SPLEEN

The weight is 640 gm.; length 18.3 cm.; width 10.8 cm.; thickness 3.8 at one end increasing to 8.4 at opposite end. The organ is of a uniform bluish-red color. The capsule is for the most part smooth with a few fine adhesions at one pole, where there is also a small circumscribed area (1.5 cm. in diameter) of thickening. The vessels of the hilum are normal. No supernumerary spleens are seen.

On section a large amount of dark fluid blood escapes. The cut surface has a uniform smooth glistening appearance of dull red color. The malpighian bodies are distinctly visible but not so large as in the normal spleen. The trabeculae are not prominent. The consistence is increased, it being almost impossible to rupture the spleen by pressure with the thumb. At one end (the larger) of the organ is a distinctly circumscribed, but not encapsulated mass (3.5 cm. in diameter), spherical in shape, which shows no malpighian bodies but does present a few minute ochre-colored areas. This area is of the same color and consistence as the rest of the spleen. On section it bulges prominently above the cut surface. The weight of the spleen after escape of fluid blood from three longitudinal incisions is 435 gm.

*Gross Diagnosis.*—Splenomegaly with area of recent infarction.

*Microscopic Appearance.*—Very slight thickening of capsule with no increase of trabeculae. The sinuses are dilated and congested. The reticulum is increased in amount and the cells of pulp appear to be decreased in number. The malpighian bodies show no change except a hyaline thickening of central arteries which is evident in arteries elsewhere. Macrophages are not numerous and deposition of pigment is not seen.

The tumor-like mass described in notes on gross appearance shows intense congestion and hemorrhage without evidence of cell destruction, and represents in all probability the results of occlusion of blood vessels at time of operation.

*Histologic Diagnosis.*—Congestion, increase of reticulum, hyaline degeneration of arteries. (The rather negative histologic appearance is in general that described for splenomegaly with congenital hemolytic jaundice.)

### METHODS

The child was kept in a private room of the University Hospital, under the constant supervision of one of us (O. H. P. P.) and with a special metabolism nurse in attendance. The complete metabolism study occupied one period of ten days and a supplementary period of five days before splenectomy and a period of ten days after splenec-

TABLE 1.—Blood Examination Before and After Splenectomy

| Date | Hb. per Cent. | Erythrocytes | Morphology of Erythrocytes | Reticulated Erythrocytes, Percentage | Resistance to Sodium Chlorid Sol. | | White Blood Cells | Percentage | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Partial Hemolysis | Complete Hemolysis | | Polys. | Lymphos. | Trans. | Monos. | Eosinos. | Basos. |
| 4/13/14* | 60 | 3,820,000 | Poikilocytosis; polychromatophilia; occasional normoblasts; anisocytosis | 4 | 0.65 | 0.425 | 6,600 | 41 | 47 | ... | 3 | 7 | 2 |
| 6/ 1/14* | 50 | 3,450,000 | Same as above | 6.1 | 0.6 | 0.375 | 9,000 | 26 | 72 | 1 | 1 | .. | .. |
| 12/ 3/14 | 23 | 2,020,000 | Same as above; no Howell-Jolly bodies | 9 | 0.625 | 0.375 | 6,100 | 49 | 46 | 2 | 2 | .. | .. |
| 1/26/15† | 33 | 2,290,000 | Same as above | ..... | 0.65 | 0.425 | 6,800 | 54 | 43 | ... | 1 | 2 | .. |
| 1/28/15 | | | | | Splenectomy | | | | | | | | |
| 2/ 2/15‡ | 38 | 3,570,000 | Not noted | ..... | ..... | ..... | 16,600 | 62 | 32 | ... | 2 | 4 | .. |
| 2/11/15‡ | 45 | 4,190,000 | Morphology much improved; no erythroblasts | ..... | ..... | ..... | 15,800 | 70 | 22 | 3 | 2 | 2 | 1 |
| 2/15/15‡ | 45 | 4,480,000 | Same as above | ..... | .... | ..... | 9,000 | 44 | 45 | ... | 10 | 1 | .. |
| 3/ 9/15† | 75 | 4,710,000 | Normal in appearance; no Howell-Jolly bodies | 1 | 0.525 | 0.35 | 14,100 | 56 | 27.5 | 7.5 | 5 | 2.5 | 1.5 |
| 4/ 9/15† | 70 | 5,070,000 | Normal | Occasional | 0.555 | 0.325 | 11,200 | 41 | 43 | 4 | 5 | 6 | 1 |

* Count by Dr. E. B. Krumbhaar.
† Count by Dr. O. H. P. Pepper.
‡ Count by hospital intern.

tomy. The first period extended from December 3 to December 14, after which the child went home for the Christmas holidays. While at home a supplementary period for the study of uric acid elimination extended from January 20 to January 24. The return to the hospital was delayed on account of the desire of the attendant physicians to improve, if possible, the blood-picture and the general condition. On January 28, two days after readmission, the spleen was removed and on Feb. 5, after a lapse of eight days, the postsplenectomy metabolism studies were begun and continued for ten days. On account of the capricious appetite of the child, it was impossible to adhere to a constant dietary, such as the Folin diet, and therefore considerable liberty was allowed. The intake was determined by weighing all foods taken and analyzing portions for nitrogen and fat. This policy was followed in both of the ten-day periods, but not in the supplementary five-day period when the child was at home. Despite the freedom as to diet, the food intake was quite constant in character from day to day, consisting in the first period essentially of milk, eggs, cereals, apple sauce, bread, crackers, potatoes, butter, sugar, rice and tapioca. During the first five days of this period, beef, chicken or fish was allowed once a day; during the second five days, these were entirely eliminated, as they were also in the supplementary period of five days before splenectomy and the ten-day period after splenectomy. Thus, except in the first five-day period, the child was on a practically purin and creatin free diet. The calorific value of the diet was adequate. During Periods I and II (Table 2), the subject received approximately 1,100 calories a day, or about 60 calories per kg. or body-weight. During Periods IV and V, the subject was on a slightly lower calorific intake, but entirely adequate, namely, 960 calories per day, or about 50 calories per kg. of body-weight.

The nitrogen of the food was estimated by the Kjeldahl-Gunning method and the fat by Soxhlet extraction. The urine was collected in twenty-four hour periods and portions passed during that period were preserved under toluene in an ice-chest. The urine was acid to litmus at all times.

In the analysis of the urine, the totatl nitrogen was determined by Kjeldahl-Gunning method; ammonia by Folin's[1] method; urea by Benedict's[2] method; uric acid by Folin's colorimetric method;[3] creatin

1. Folin, O.: Eine neue Methode zur Bestimmung des Ammoniaks im Harne, Ztschr. f. physiol. Chem., 1902-03, xxxvii, 161.

2. Benedict, S. R.: The Estimation of Urea, Jour. Biol. Chem., 1910-11, viii 405.

3. Folin, O., and MacCallum, A. B., Jr.: A New Method for the (Colorimetric) Determination of Uric Acid in Urine, Jour. Biol. Chem., 1912-13, xiii, 361; Folin, O., and Denis, W.: On the Colorimetric Determination of Uric Acid in Urine, Jour. Biol. Chem., 1913, xiv, 95.

and creatinin by Folin's method[4] and the hydrogen ion concentration according to Henderson's technic.[5]

In the study of the feces the fat content was determined by the Folin-Wentworth method;[6] the iron was estimated by Neumann's method;[7] nitrogen by the Kjeldahl-Gunning method and urobilin by a slight modification of the method recommended by Wilbur and Addis.[8]

Period III (Table 2) was considered a desirable control on account of the high figures for uric acid obtained in the first and second periods. The analyses in this period were, therefore, limited to those determinations of special interest in this connection.

In Table 2 are presented the results of the study of nitrogen metabolism.

*Nitrogen Metabolism.*—During Periods I and II, before splenectomy, the subject was in a slight plus balance. After splenectomy, during Period IV, a great retention of nitrogen occurred, although the intake varied but little from the previous periods and the subject was not gaining in weight. The logical explanation of this change would be either of the following: (1) reparative processes going on in the body, as indicated by the rapid regeneration of hemoglobin and red cells, or (2) the removal of toxic influences leading to an improvement in the general nutritive condition and thus to the normal retention in a healthy child. The utilization of protein was good at all times. The average percentage of total nitrogen eliminated as urea was 85.5 before splenectomy, and 87.2 afterwards, figures within the normal range. The differences of the averages may possibly be explained by the changes in one of the other nitrogen constituents of the urine, namely, uric acid.

*Uric Acid.*—The uric acid output was exceedingly high in Periods I and II. Period I was not purin free. Period II, however, was practically free from purin intake, notwithstanding which the uric acid output continued on its high level. The urines were highly colored and when allowed to stand gave a precipitate of uric acid crystals. In view of this high elimination of uric acid a supplementary study was made (Period III) during which the subject was again placed

4. Folin, O.: Approximately Complete Analyses of Thirty "Normal" Urines, Am. Jour. Physiol., 1905, xiii, 45.

5. Henderson, J. L., and Palmer, W. W.: On the Intensity of Urinary Acidity in Normal and Pathological Conditions, Jour. Biol. Chem., 1912-13, xiii, 393.

6. Folin, O., and Wentworth, A. H.: A New Method for the Determination of Fat and Fatty Acids in Feces, Jour. Biol. Chem., 1910, vii, 421.

7. Neumann, A.: Einfache Veraschungsmethode (Säuregemisch-Veraschung), Ztschr. f. physiol. Chem., 1902-03, xxxvii, 114; ibid., 1904-05, xliii, 32.

8. Wilbur, R. L., and Addis, T.: Urobilin, Its Clinical Significance, The Archives Int. Med., 1914, xiii, 235.

TABLE 2.—METABOLISM IN CONGENITAL HEMOLYTIC ICTERUS BEFORE AND AFTER SPLENECTOMY

| Period | Date | Wt. in Kg. | Nitrogen Intake, Gm. | Urine | | | | | | | | | | Feces; Total Nitrogen, Gm. | Total Nitrogen Output, Gm. | Nitrogen Balance, Gm. | Clinical Notes and Temperature |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Amt., c.c. | Sp. Gr. | Hydrogen Ion Conc.* | Total Nitrogen, Gm. | Urea, Gm. | Ammonia, Gm. | Uric Acid, Gm. | Totalt Creatinin, Gm. | Creatinin, Gm. | Creatin, Gm. | | | | |
| I | 12/ 4/14 | 17.7 | 6.45 | 480 | 1.022 | 6.15 | 6.00 | 5.25 | 0.36 | 0.468 | 0.476 | 0.289 | 0.217 | 0.54 | 6.63 | −0.18 | 98.2 |
| | 12/ 5/14 | .... | 9.00 | 530 | 1.018 | 5.70 | 5.46 | 4.53 | 0.33 | 0.468 | 0.398 | 0.235 | 0.154 | 0.54 | 6.00 | +3.00 | 98.4 |
| | 12/ 6/14 | .... | 5.16 | 480 | 1.020 | 5.50 | 4.99 | 4.18 | 0.32 | 0.468 | 0.309 | 0.226 | 0.096 | 0.54 | 5.53 | −0.37 | 101.4 |
| | 12/ 7/14 | .... | 5.66 | 400 | 1.025 | 5.85 | 6.38 | 5.54 | 0.26 | 0.516 | 0.385 | 0.270 | 0.133 | 0.54 | 6.92 | −1.26 | 99.6 |
| | 12/ 8/14 | .... | 6.47 | 550 | 1.019 | 6.15 | 6.54 | 5.60 | 0.32 | 0.490 | 0.405 | 0.261 | 0.167 | 0.54 | 7.08 | −0.61 | 100.2 |
| | Average | .... | 6.55 | 488 | 21 | 5.87 | 5.89 | 5.02 | 0.32 | 0.482 | 0.389 | 0.256 | 0.153 | 0.54 | 6.24 | +0.12 | ..... |
| II | 12/ 9/14 | .... | 4.91 | 280 | 1.030 | 6.15 | 3.96 | 3.41 | 0.19 | 0.410 | 0.271 | 0.191 | 0.093 | 0.52 | 4.48 | +0.43 | 99.6 |
| | 12/10/14 | .... | 6.12 | 500 | 1.020 | 6.30 | 5.18 | 4.40 | 0.31 | 0.544 | 0.369 | 0.289 | 0.093 | 0.52 | 5.70 | +0.42 | 100.4 |
| | 12/11/14 | .... | 4.12 | 270 | 1.028 | 6.15 | 3.00 | 2.75 | 0.15 | 0.544 | 0.211 | 0.191 | 0.023 | 0.52 | 3.52 | +0.60 | 99.8 |
| | 12/12/14 | .... | 5.03 | 320 | 1.026 | 6.00 | 4.07 | 3.43 | 0.20 | 0.460 | 0.271 | 0.241 | 0.035 | 0.52 | 4.59 | +0.44 | 100.2 |
| | 12/13/14 | 18.2 | 4.90 | 360 | 1.027 | 6.00 | 4.98 | 4.20 | 0.24 | 0.788 | 0.320 | 0.270 | 0.058 | 0.52 | 5.50 | −0.60 | 98.4 |
| | Average | .... | 5.02 | 346 | 26 | 6.12 | 4.24 | 3.64 | 0.22 | 0.540 | 0.288 | 0.236 | 0.060 | 0.52 | 4.76 | +0.26 | ..... |
| III | 1/20/15 | .... | .... | 440 | 1.019 | .... | 4.59 | .... | .... | 0.400 | 0.279 | 0.225 | 0.063 | | | | |
| | 1/21/15 | .... | .... | 410 | 1.029 | .... | 4.29 | .... | .... | 0.560 | 0.270 | 0.209 | 0.071 | | | | |
| | 1/22/15 | .... | .... | 415 | 1.033 | .... | 3.51 | .... | .... | 0.520 | 0.259 | 0.207 | 0.060 | | | | |
| | 1/23/15 | .... | .... | 690 | 1.019 | .... | 3.81 | .... | .... | 0.460 | 0.245 | 0.215 | 0.035 | | | | |
| | 1/24/15 | .... | .... | 500 | 1.024 | .... | 4.31 | .... | .... | 0.614 | 0.300 | 0.270 | 0.085 | | | | |
| | Average | .... | .... | 491 | 25 | .... | 4.10 | .... | .... | 0.511 | 0.271 | 0.225 | 0.063 | | | | |
| | 1/28/15 | | | Splenectomy | | | | | | | | | | | | | |
| IV | 2/ 6/15 | 18.2 | 7.08 | 540 | 1.023 | 6.00 | 5.61 | 4.95 | 0.22 | 0.326 | 0.300 | 0.203 | 0.113 | 0.35 | 5.96 | +1.12 | 99.6 |
| | 2/ 7/15 | .... | 6.23 | 560 | 1.020 | 6.00 | 4.71 | 4.08 | 0.21 | 0.294 | 0.283 | 0.180 | 0.119 | 0.35 | 5.06 | +1.17 | 99.0 |
| | 2/ 8/15 | .... | 6.41 | 570 | 1.020 | 6.00 | 4.80 | 4.16 | 0.19 | 0.294 | 0.311 | 0.197 | 0.132 | 0.35 | 5.15 | +1.26 | 99.8 |
| | 2/ 9/15 | .... | 4.97 | 570 | 1.020 | 6.70 | 3.63 | 3.11 | 0.12 | 0.290 | 0.234 | 0.176 | 0.109 | 0.35 | 3.98 | +0.99 | Bronchitis 103.2 |
| | 2/10/15 | .... | 4.99 | 450 | 1.023 | 6.80 | 3.06 | 2.68 | 0.10 | 0.226 | 0.194 | 0.176 | 0.063 | 0.35 | 3.41 | +1.58 | 102.2 |
| | Average | .... | 5.94 | 544 | 21 | 6.30 | 4.36 | 3.80 | 0.17 | 0.286 | 0.264 | 0.172 | 0.107 | 0.35 | 4.71 | +1.22 | ..... |
| V | 2/11/15 | .... | 6.30 | 630 | 1.020 | 5.70 | 6.15 | 5.37 | 0.21 | 0.296 | 0.337 | 0.287 | 0.058 | 0.40 | 6.55 | −0.35 | 99.4 |
| | 2/12/15 | .... | 5.27 | 350 | 1.024 | 5.50 | 4.88 | 4.34 | 0.23 | 0.272 | 0.288 | 0.206 | 0.041 | 0.40 | 5.23 | +0.04 | 98.8 |
| | 2/13/15 | .... | 4.83 | 530 | 1.022 | 6.00 | 5.64 | 4.83 | 0.31 | 0.320 | 0.290 | 0.253 | 0.043 | 0.40 | 6.04 | −1.21 | 99.0 |
| | 2/14/15 | .... | 5.38 | 360 | 1.032 | 6.80 | 4.08 | 3.54 | 0.14 | 0.224 | 0.238 | 0.195 | 0.050 | 0.40 | 4.48 | +0.90 | Otitis media 99.0 |
| | 2/15/15 | 17.5 | 6.17 | 430 | 1.025 | 6.70 | 4.73 | 4.13 | 0.18 | 0.218 | 0.248 | 0.203 | 0.052 | 0.40 | 5.13 | +1.04 | 99.0 |
| | Average | .... | 5.57 | 460 | 25 | 6.14 | 5.09 | 4.44 | 0.23 | 0.266 | 0.272 | 0.228 | 0.049 | 0.40 | 5.49 | +0.08 | ..... |

* Expressed as negative logarithms.
† Includes preformed creatinin and creatin as creatinin.

on a purin-free dietary, consisting mainly of milk, eggs, shredded wheat and custard. In this period the high output of uric acid, presumably almost entirely endogenous, still persisted. This average (Periods II and III), 0.530 gm. of uric acid, is very close to the highest average of uric acid output of an adult on a purin-free diet. Few figures for normal uric acid output in children are to be found in the literature. Closson[9] in a child of about 7 years of age found an average output of 0.23 gm. on a purin-free diet.

After splenectomy the average output of uric acid in Periods IV and V decreased 47 per cent. from the average of Periods II and III before splenectomy. It will be remembered that the diets of all these periods were purin free. The appearance of the urine in these later periods was markedly altered, the dark-red color being replaced by a pale yellow, with never a spontaneous precipitate of uric acid.

*Hydrogen Ion Concentration.*—On the same general diet the hydrogen ion concentration of the urine remained constant before and after splenectomy. During Period I, on a mixed diet, an average of 5.87 falls within the average (5.94) of Henderson and Palmer.[10] On the purin-free diet yielding a more alkaline ash, the hydrogen concentration before operation is in agreement with that after the operation. It is of interest here to note that the hydrogen concentration is not appreciably altered by changes in uric acid content of urine, although, as shown by Blatherwick[11] the ability of a urine to dissolve uric acid is a function of the hydrogen ion concentration.

*Ammonia Nitrogen.*—The ammonia nitrogen in our experiments shows no variations from the normal. Its close agreement with hydrogen ion concentration may be noted, thus a rise in the hydrogen ion concentration is associated with a fall in the ammonia output and vice versa.

*Creatinin and Creatin.*—The creatinin output showed a great constancy in Periods II and III, before splenectomy, on the purin-free diet. During Period I, on a mixed diet, the output is slightly above the average of these periods. During Period IV, after the operation, the creatinin output fell to its lowest point, a decrease of 25 per cent. from the average of the other purin-free periods. When the total creatinin, that is preformed creatinin and creatin as creatinin, output of each period is compared, one readily sees that the total creatinin, in all of the periods on creatin-free diet, shows a remarkable constancy.

9. Closson, O. E.: The Elimination of Creatinin, Am. Jour. Physiol., 1906, xvi, 252.

10. Henderson, L. J., and Palmer, W. W.: On the Several Factors of Acid Secretion, Jour. Biol. Chem., 1914, xvii, 305.

11. Blatherwick, N. R.: The Specific Rôle of Foods in Relation to the Composition of the Urine, The Archives Int. Med., 1914, xiv, 409.

As will be seen from an inspection of the tables, the decrease of creatinin was accompanied by an increase of the creatin amounting to 91 per cent. of the average. Why, in Period IV, the partition of creatinin and creatin changed without an appreciable change of total creatinin is difficult to state. During the last two days of this period the patient suffered from a bronchitis with a rise in temperature, but that these are explanatory factors hardly seems plausible.

As regards creatin output, with the exception of the first period, which was not that of a creatin-free diet, the output shows a fair degree of regularity. The increased output in Period IV has already been pointed out.

There is a paucity of data on the creatinin and creatin output of children on controlled diets. The results obtained by Folin[12] on his children offer figures which may serve for comparison.

The great constancy of our total creatinin (including preformed creatinin and creatin as creatinin) output leads us to believe that for the purpose of comparison in children this is the figure to be used rather than the relative or absolute amounts of creatin or creatinin. This point is now under investigation by one of us (S. G.) and will be reported in a later communication. On the basis of this comparison this total creatinin output agrees very well with other published figures for children. The change in the partition of creatin and creatinin will also be the subject of this later paper. We believe our creatin and creatinin figures to be within the range of normal variations.

*Fats.*—The total intake of fats and the separation of fats in the feces are shown in Table 3. In this table Periods I and II represent the presplenectomy and Periods IV and V the postsplenectomy studies. Each period represents five days.

TABLE 3.—Fat Determinations

| Period | Total Intake Gm. | Total Output Gm. | Per Cent. of Fat Utilized | Total Output Fatty Acids Including Soaps, Gm. | Per Cent. Fatty Acids in Total Fat Output | Total Output Neutral Fats | Per Cent. Neutral Fats in Total Fat Output |
|---|---|---|---|---|---|---|---|
| Before Splenectomy: | | | | | | | |
| I | 222 | 8.88 | 96.01 | 6.8 | 76.8 | 2.1 | 23.2 |
| II | 223 | 7.57 | 96.62 | 5.1 | 67.0 | 2.5 | 33.0 |
| After Splenectomy: | | | | | | | |
| IV | 227 | 13.56 | 94.04 | 10.1 | 74.4 | 3.5 | 25.6 |
| V | 209 | 13.55 | 94.98 | 9.8 | 72.3 | 3.7 | 27.7 |

12. Folin, O.: On Creatinin in the Urine of Children, Jour. Biol. Chem., 1912, xi, 251.

The metabolism of fats shows no abnormal variations. The fat utilization is good, and well within normal limits. As pointed out by Folin and Wentworth,[6] as total fat increases more of that fat is put out as fatty acids (including soaps).

*Iron.*—Table 4 presents the results of the examination of the feces for iron. As the iron in human urine seldom exceeds 0.001 mg., the urine is not included. Analyses for iron were made on duplicate samples of dried feces representing periods of ten days, before and after splenectomy, respectively.

TABLE 4.—IRON ELIMINATION IN FECES

| Period | Total Intake Period Mg. (calculated) | Total Output Period Mg. | Intake per Day Mg. | Output per Day Mg. |
|---|---|---|---|---|
| Before Splenectomy<br>I<br>II | 37.69 | 82.99 | 3.77 | 8.29 |
| After Splenectomy<br>IV<br>V | 45.61 | 41.11 | 4.56 | 4.11 |

Thus the first ten days correspond to Periods I and II and the second ten days to Periods IV and V. Periods II, IV, and V represent essentially the same diet. The figures for iron intake were calculated from published records[13] of iron content of foods, hence no claim is made for the extreme accuracy of those figures. They merely serve to show that the iron content of the diet agreed very closely and would not account for the large difference in output. Those differences in output before and after splenectomy amounted to about 40 per cent. decrease. That the large output of iron in the period before splenectomy is due to the increased elimination of iron consequent on the excessive destruction of red cells, seems the most plausible explanation. The decreased elimination after splenectomy, with a close agreement of intake and output, show a cutting off of this loss and presumably a return to normal elimination.

*Urobilin.*—Our interest in the urobilin problem has been limited to the influence of the absence of the spleen on the elimination of this substance. In the urine qualitative tests for urobilin gave negative results throughout the experiment. At one time in a concentrated urine a faintly positive reaction was obtained with Ehrlich's reagent. The large bulk of this constituent was in the feces. Because of the small bulk of the child's feces, and the necessity of utilizing considerable portions for other determinations, the use of the wet feces for

13. Sherman, H. C.: Food Products. Macmillan: New York, 1914.

urobilin determination was impracticable. The feces were therefore dried in the usual way and placed immediately in well-stoppered bottles. At the end of the experiment the feces of Periods I and II, before splenectomy, and IV and V, after splenectomy, were combined for urobilin estimation. In view of the previous work[8] on this substance, it was to be expected that some of the urobilin would be destroyed, or that most of the urobilinogen would be converted into urobilin but whether or not this took place we have no means of determining. The fact remains that considerable urobilinogen was still present at the time of analysis. Inasmuch, however, as both sets of feces were treated alike this was a more or less constant factor. Five gm. of feces were extracted with 100 c.c. of acid alcohol and treated as described in method as outlined by Wilbur and Addis.[8] The dilution for total mass of feces was then calculated. The dilution follows:

Dilution required for extinction of urobilinogen and urobilin absorption bands: Periods I and II (combined) 71,250; Periods IV and V (combined) 7,954.

These results are in accord with those described by Eppinger,[14] who found, in a variety of clinical conditions accompanied by rapid blood destruction, that the urobilin in the stools sank to normal after splenectomy.

## DISCUSSION

The literature concerning the relation of the spleen to metabolism may be considered under five heads: (1) studies both before and after splenectomy for disease of the spleen in man; (2) studies in man after splenectomy; (3) studies of congenital hemolytic jaundice; (4) studies of anemia; (5) studies of the effect of removal of the normal spleen in animals.

1. In only three instances have metabolic studies been made both before and after splenectomy for diseases of the spleen in man. Two of these are Umber's studies of Banti's disease and the third Minot's study of pernicious anemia. Umber studied two individuals splenectomized for Banti's disease and Minot one in whom the spleen was removed as a last resort in pernicious anemia. One of Umber's subjects[14] was a boy of 15 with anemia and icterus. The postoperative period of study covered twelve days and began twenty-four days after the operation. The diet was purin free and a fully controlled metabolic study was made. The results showed no pronounced variation in the distribution of the urinary constituents which could be attributed to the absence of the spleen. Umber makes a point, however, of the fact

14. Eppinger, H.: Zur Pathologie der Milzfunction, Berl klin. Wchnschr., 1913, 1, 1509; 1572.

that after removal of the spleen it was easier to obtain nitrogen equilibrium, attributing the pathologic destruction of protein to a toxic cause. His figures show also a somewhat greater output of purins before the operation than after. In another case of Banti's disease described in this report[15] the "toxic" disturbance of metabolism was not present and splenectomy was not done. In a later study[16] Umber describes a young man of 21 suffering from what he considers as the "toxic" type of Banti's disease. Splenectomy led to striking improvement. The metabolism study of this case was limited to a comparison of total nitrogen intake and output before and after splenectomy. The results confirm his former observation, namely, that a persistent negative balance before splenectomy changes to a positive balance after splenectomy. The postsplenectomy study was made three months after operation. Minot's[16] patient was a colored woman aged 35, on whom metabolic studies were begun fifteen days after splenectomy and transfusion. The figures given for five twenty-four hour periods before and six after splenectomy are not for consecutive days. The examination included total nitrogen in urine and feces and urea and ammonia in the urine. The chief results were a change from a slight negative to a slight positive nitrogen balance and an increase in percentage of urea after splenectomy. The uncertainty of the food intake in the period before splenectomy, the low caloric intake and the shortness of consecutive periods of observation, make these balances of doubtful value.

2. Lo Monaco[18] found in a splenectomized individual no important change in uric acid elimination.

Mendel and Gibson,[19] in the case of a man with enlarged spleen and secondary anemia following malaria, studied the metabolism (total nitrogen, urea, uric acid, ammonia, phosphorus, chlorids and sulphates) after splenectomy, but found no striking variation from the normal distribution of the urinary components. These authors had no presplenectomy studies for comparison.

Likewise, Moraczewski,[20] who made some studies of both nitrogenous and mineral metabolism in a man of 51, seven months after

15. Umber, F.: Zur Pathogenese der "Banti'schen Krankheit" mit besonderer Berücksichtigung des Stoffumsatzes vor und nach der Splenectomie, Ztschr. f. klin. Med., 1904, lv, 289.

16. Umber, F.: Zur Pathologie der Bantischen Krankheit, München. med. Wchnschr., 1912, lxix, 1478.

17. Minot, G. R.: Nitrogen Metabolism Before and After Splenectomy in a Case of Pernicious Anemia, Bull. Johns Hopkins Hospital, 1914, xxv, 338.

18. Lo Monaco, D.: Osservazioni sull'escrezione e sulla formazione dell'acido urico nell'organismo, Bull. d. Soc. Lancis. d. ospedali Roma, 1894, xiv, 102. Reference in Schmidt's Jahrbüch., 1896, cclii, 109.

19. Mendel, L. B., and Gibson, R. B.: Observations on Nitrogenous Metabolism in Man After Removal of the Spleen, Am. Jour. Physiol., 1907, xviii, 201.

20. Moraczewski, W.: Fieberverlauf bei einem Splenectomirten, Berl. klin. Wchnschr., 1903, xl, 1002.

splenectomy for "spleen tumor" (malarial), found no important variations. His observations, however, were few in number and were made in the course of an attack of pneumonia which rendered matters of diet and control difficult.

3. The only carefully conducted and complete study of the metabolism in congenital hemolytic icterus is, so far as we are aware, that of McKelvy and Rosenbloom.[21] The patient, a girl aged 11, on a Folin diet, was studied for six days. The total nitrogen, fat and mineral constituents of the food were determined and both urine and feces studied as to nitrogenous and mineral constituents and the feces as to fat. During a period of six days there was a loss of 4.06 gm. of nitrogen, which the authors suggest may be due to a toxogenic destruction of protein. The nitrogen partition of the urine was normal except in the case of the uric acid nitrogen, which was increased. This increase, the writers state, might be due to the increased liberation of nucleoproteins through hemolysis of the erythrocytes. The study of mineral metabolism showed a loss of sulphur, iron, calcium and magnesium and a retention of phosphorus. The fat metabolism was normal. No metabolism studies were made after splenectomy.

In a woman, aged 39, with "chronic family jaundice," Tileston and Griffen[22] studied, for three successive days and an added odd day, the output of ammonia, urea, creatin and creatinin on a purin-free and creatin-free diet. They found the elimination of creatinin and urea to be essentially normal, ammonia somewhat high, and uric acid distinctly increased. However, it should be noted that only one determination of uric acid was made.

Haal[23] in a case of family hemolytic jaundice, found an increased excretion of uric acid and of iron.

4. As the changes in metabolism in various types of anemia have recently been summarized by Minot,[17] we will not present this literature in detail. The opposing views are represented by Rosenqvist and von Noorden. Rosenqvist,[24] in pernicious anemia and bothriocephalus anemia, found variations in nitrogen elimination, with periods of alternate increased and decreased excretion. In bothriocephalus anemia a well-marked loss of nitrogen while the worm was in the body was

21. McKelvy, J. P., and Rosenbloom, J.: Metabolism Study of a Case of Congenital Hemolytic Jaundice with Splenomegaly, THE ARCHIVES INT. MED., 1915, xv, 227.

22. Tileston, W., and Griffen, W. A.: Chronic Family Jaundice, Am. Jour. Med. Sc., 1910, cxxxix, 847.

23. Haal: Quoted by Minkowski in Modern Clinical Medicine, Diseases of the Digestive System, p. 349.

24. Rosenqvist, E: Ueber den Eiweisstoffwechsel bei der perniciösen Anämie, Ztschr. f. klin. Med., 1903, xlix, 193.

followed, after removal of the worm, by a retention. Rosenqvist concluded that in both types of anemia a pathologic decomposition of protein is present. Von Noorden[25] opposes this view and as a result of his studies concludes that protein decomposition is not increased as the result of anemia of the ordinary types. The variations in output he believes may be explained by the alimentary and renal disturbances which accompany anemia. That an increased output of nitrogen may occur in anemia due to parasites is admitted, as is also the possibility in non-parasitic anemias of a temporary increase in the output of nitrogen as the result of a sudden destruction of large masses of red cells.

As to uric acid output, von Noorden refers to Rosenqvist's high figures and to other observations and concludes that as a rule in anemia the output is normal but sometimes rises, as in Rosenqvist's work, to twice the normal amount.

It is noteworthy that in bothriocephalus anemia, Rosenqvist found that after removal of the parasite, the purin output increased temporarily and then returned to normal. This temporary increase he explains as due to the regeneration and increased metabolic activity of the blood and somatic cells consequent on the removal of the toxic agent. As the cells recovered their normal equilibrium the output of the purins fell to normal level.

Halpern,[26] studying one case of pernicious anemia and one of splenic anemia, found normal values for the various urinary constituents. His figures for purin output are in no way abnormal.

5. The literature of splenectomy in man for conditions other than chronic anemia, as, for example, gunshot wound, rupture, cyst, etc., shows that no metabolism studies have been made in such conditions. Conclusions concerning the effect on metabolism of removal of the normal spleens in the normal individual must, therefore, be based on observations on animals.

Splenectomy in animals (Paton,[27] Mendel and Jackson,[28] Austin and Ringer,[29] Verzár,[30] Korenchevski[31]) offers no evidence to show

25. Von Noorden, C.: Metabolism and Practical Medicine, II, p. 360.

26. Halpern, M.: Zur Frage der Stickstoffvertheilung im Harn in pathologischen Zuständen, Ztschr. f. klin. Med., 1903, l, 355.

27. Paton, N.: Studies of the Metabolism in the Dog Before and After Removal of the Spleen, Jour. Physiol., 1900, xxv, 443.

28. Mendel, L. B., and Jackson, H. C.: On Uric Acid Formation After Splenectomy, Am. Jour. Physiol., 1900, iv, 163.

29. Austin, J. H., and Ringer, A. I.: The Influence of Phlorizin on a Splenectomized Dog, Jour. Biol. Chem., 1913, xiv, 139.

30. Verzár, F.: Die Grösse der Milzarbeit, Biochem. Ztschr., 1913, liii, 69.

31. Korenchevski, V. G.: Nitrogenous and Gaseous Metabolism in Spleenless Animals, Russky Vratch, 1910, ix, 1441.

that the spleen has an important influence on metabolism, though Richet[32] states that in order to maintain their weight splenectomized animals require a larger quantity of food than do normal animals. In these experiments the dog, and rarely, the cat, were used.

The literature contains no records of the examination of the feces for fat before and after splenectomy. Tileston and Griffen, in one of their cases of chronic family jaundice, studied, without result, the fats of a single stool. McKelvy and Rosenbloom in their case of congenital hemolytic jaundice report normal fat metabolism.

The literature of iron metabolism is, at best, unsatisfactory, and this is especially true of work on the relation of the spleen to iron metabolism. Most of the work is based on Schmidt's[33] conclusions, drawn from the results of the feeding of iron-poor food to normal mice, that the organism possesses great power of conserving the iron and of re-utilizing it through some form of intermediary metabolism. In this connection Schmidt regards the liver as the depot for iron from the food, and the spleen as the depot for iron from tissue and erythrocyte catabolism.

On the basis of experiments on splenectomized dogs, Asher and his associates (Grossenbacher[34] and Zimmermann[35]) claim to have demonstrated an increased elimination of iron, often double that of normal animals, at various intervals after splenectomy. These studies were made on young puppies and the observations correspond to periods of a few weeks, two months and ten months after splenectomy.

Austin and Pearce[36] in a series of five dogs in which the iron elimination was studied before and within two weeks after splenectomy, found a slight increase in iron output in three and practically no change in two. When longer periods had elapsed after splenectomy, as one, nine and twenty months, no evidence was secured of an increase in iron output. Such observations, they concluded, do not support the view that the spleen exerts a constant and important influence on iron metabolism.

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32. Richet, C.: Des effets de l'ablation de la rate sur la nutrition chez les chiens, Jour. Physiol. et d. Path. gen., 1912, xiv, 689; ibid., 1913, xv, 579.

33. Schmidt, M. B.: Ueber die Organe des Eisenstoffwechsels und die Blutbildung bei Eisenmangel, Verhandl. d. Deutsch. path. Gesellsch., 1912, xv, 91.

34. Asher, L., and Grossenbacher, H.: Beiträge zur Physiologie des Drüsen, Untersuchungen über die Funktion der Milz, Biochem. Ztschr., 1909, xvii, 78.

35. Asher, L., and Zimmermann, R.: Beiträge zur Physiologie der Drüsen, Fortgesetzte Beiträge zur Funktion der Milz als Organ des Eisenstoffwechsels, Biochem. Ztschr., 1909, xvii, 297.

36. Austin, J. H., and Pearce, R. M.: The Relation of the Spleen to Blood Destruction and Regeneration and to Hemolytic Jaundice, XI. The Influence of the Spleen on Iron Metabolism, Jour. Exper. Med., 1914, xx, 122.

No observations in man, on iron elimination before and after splenectomy, are at hand. Bayer[37] in the study of iron elimination after splenectomy for rupture of the spleen and Banti's disease compared his results with those obtained in normal individuals. He found an increased output soon after splenectomy in the case of spleen rupture, but later the elimination returned to normal; in the case of Banti's disease the elimination did not differ from the control. McKelvy and Rosenbloom's studies of congenital hemolytic jaundice before splenectomy show that the elimination of iron in this disease is, on the basis of normal figures in the literature, increased. This increase they explain as due to the great destruction of red cells.

From this brief review of the literature it is evident that in anemia, with or without splenic disease, the majority of investigators have experienced difficulty in obtaining a nitrogen balance. Umber[15, 16] in his study of Banti's disease, Minot,[17] in pernicious anemia, McKelvy and Rosenbloom[21] in congenital hemolytic icterus, and Rosenqvist[24] in pernicious anemia and bothriocephalus anemia all report a pathologic destruction of protein. Umber[15] goes so far as to urge this "toxic destruction" as a criterion for operation. Von Noorden[25] alone opposes this theory of increased destruction of protein in anemia. In the case we report, no difficulty was experienced in obtaining a positive nitrogen balance before the operation; feeding was not forced, the patient merely satisfying his natural desires for food. Nevertheless, the increased retention after the operation on the same nitrogen intake would appear to support the theory that some toxogenic influence had been removed. To this influence, however, must be added as a cause of retention the higher level of reparative processes going on in the body, as, for example, in the bone marrow and possibly other organs. The difference between our slight positive balance and Umber's marked negative balance before operation may possibly be a difference dependent on the age of the individuals.

Our subject, it will be remembered, was a child, whose natural tendency would be to retain nitrogen for growth, and it is not difficult to imagine that this tendency would affect the toxic destruction to a greater degree than in an adult. (The patients in Umber's cases were 15 and 21 years of age.)

As regards the elimination of uric acid in anemia, with or without disease of the spleen, one finds the general view to be that the elimination is high. Rosenqvist (in 1903) as a result of his studies of

37. Bayer, R.: Untersuchungen über den Eisenstoffwechsels nach der Splenectomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1910, xxi, 335; Weitere Untersuchungen über die Funktionen der Milz, vornemlich ihre Rolle im Eisenstoffwechsel mit besonderer Berücksichtigung des Morbus Banti, ibid., 1913, xxvii, 311.

pernicious anemia and bothriocephalus anemia, reports large outputs of uric acid, sometimes twice the normal amount. He finds that after the removal of the worm in the latter condition, there is first an increased elimination of purins and then a return to the normal. His explanation for this is an increased metabolic activity of the blood and somatic cells following the removal of the toxic agent. In our case, after removal of the spleen, we found the reverse condition, an immediate drop to normal. That an increase took place between the time of operation and the beginning of our first postsplenectomy period (8 days after operation) we cannot say. When, however, one inspects the results of blood examination after operation, it is observed that the increase in red cells and hemoglobin was steady and gradual, no greater during the first eight days after operation than during the subsequent ten days of our metabolism period; so that regenerative processes were at best gradual.

Umber, in his studies, does not report uric acid output, but groups his findings under total purins of which he found, in Banti's disease, a somewhat greater output before operation than after. Haal, in family hemolytic jaundice, found an increased excretion of uric acid. Von Noorden gives as his opinion, based on a review of the literature, that in anemia the output may be normal, but is sometimes increased. Lo Monaco, and Mendel and Gibson report no change in uric acid excretion after splenectomy but present no presplenectomy studies for comparison.

In congenital hemolytic icterus, McKelvy and Rosenbloom report higher uric acid output, but present no studies after splenectomy. They give as an explanation for the increased output, the greater formation of nucleoprotein resulting from the destruction of red cells. Their explanation seems to be inadequate, for it is difficult to imagine the destruction of red cells as being the sole source of this large output of purin. It may, to some extent, be a factor, but the toxic influence on the somatic cells generally, of bile products would appear to be a factor of greater importance. The sallow discoloration of the skin in the disease is indication of the general dissemination of substance absorbed from the bile and our knowledge of the toxic influence of bile constituents offers an explanation for a widespread state of cell degeneration and consequent repair which would readily explain the increased output of products of nuclein metabolism.

Our findings concerning the increased elimination of iron before splenectomy are in practical accord with those of McKelvy and Rosenbloom and can be explained as due to the increased blood destruction. Other comparisons are impossible, as in no study before ours has iron elimination been studied both before and after splenectomy. Bayer's

studies after splenectomy for spleen rupture and Banti's disease do not include presplenectomy studies but comparisons with normal individuals. In his case of Banti's disease the iron elimination after splenectomy did not differ from that of the normal control; in the cases of spleen rupture a slight increased elimination was followed by a return to normal.

The results of our study of urobilin are in accord with the older views as to the source of this substance, that is excessive blood destruction, and also with the views of Eppinger concerning the decrease of urobilin after splenectomy for various diseases of the blood. It is interesting that in this case of acholuric icterus the mass of urobilin was in the feces and not in the urine.

## SUMMARY

In a child with congenital hemolytic icterus splenectomy was followed by a disappearance of the discoloration of the skin, a rapid improvement in the condition of the blood and a striking improvement in general health.

Metabolism studies before and after splenectomy gave the following results:

1. A slight positive nitrogen balance before splenectomy was followed by an increased retention eight days after operation.
2. The output of uric acid showed a decrease of 47 per cent. after operation.
3. In the period directly after operation a change in the partition of creatinin and creatin elimination occurred; the total creatinin, however, showing but slight change.
4. Other urinary nitrogen constituents showed no variations from the normal, and no change was found in the hydrogen ion concentration.
5. The utilization of nitrogen was good at all times.
6. Fat metabolism was normal.
7. There was a large loss of iron through the feces before splenectomy followed by a decided decrease (40 per cent.) after operation.
8. The excretion of urobilinogen and urobilin in the feces was markedly diminished after splenectomy; the amount after operation was about one-ninth of that excreted before splenectomy.

# THE EFFECT OF HEMORRHAGE AND OF OCCLUSION OF THE CAROTID ARTERIES ON VASOMOTOR IRRITABILITY *

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The mechanism which controls blood pressure is one of the most complicated with which the physician has to deal. Arterial pressure depends on two factors—the amount of excitation and the irritability and the resistance to flow in the blood vessels. Peripheral resistance in turn depends to some extent on the elasticity of the arterial walls and the relative viscosity of the blood, but more particularly on the aggregate bore of the terminal arterial channels—the arterioles. This bore is quite variable and depends on several factors. The chemical composition of the blood itself has an important influence on the muscle cells of the vessels. The presence or absence of epinephrin is an example in point. The concentration of carbon dioxid is another factor the importance of which has only lately begun to be realized. The temperature of the blood is probably also of some practical significance. But the most important influence is that exerted by the *vasomotor nervous system* on the muscle cells of the arterioles. This system is essentially an intricate complex of reflex arcs. The term *vasomotor apparatus* is used in this paper to include both the nervous structures proper and the muscle cells to which the nerve impulses are finally delivered.

The activity of the vasomotor apparatus at any given moment depends on two factors—the amount of excitation and the irritability of the various parts of the apparatus. For example, blood pressure may be lowered either by putting the subject at rest, i. e., lessening the excitation, or by narcotizing some essential part of the apparatus. Although a great amount of work has been done on the blood pressure as an entity, few attempts have been made to study specifically the influence of different conditions on *vasomotor irritability*. It is altogether likely that a clean-cut knowledge of this matter would aid materially in giving us an understanding of the essential nature of

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surgical shock and sleep as well as various clinical cases of hypertension and hypotension.

For some time past the efforts of our laboratory have been directed largely to studies along this line. Particularly, the relation of various ductless glands to vasomotor irritability[1] has been investigated. This paper, which is a continuation of the series, is concerned with the influence of certain circulatory conditions themselves on the vasomotor reactions.

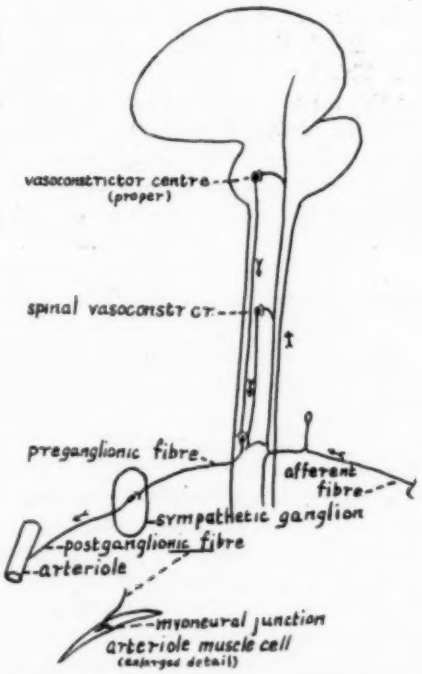


Fig. 1.—Diagrammatic scheme of the vasomotor apparatus.

The accompanying sketch (Fig. 1) illustrates the conception of the vasomotor apparatus on which our studies have been based. Although it involves nothing that is new it is included for what it may be worth in adding clearness. Suppose that a given impulse, for instance, one due to a pin prick on the leg, is destined to be delivered to the arteriole walls and cause a rise of blood pressure. The impulse travels over an afferent fiber to the spinal cord. In the cord it may go either upward to the vasoconstrictor center in the medulla or may go directly to a

1. Hoskins and Wheelon: Am. Jour. Physiol., 1914, xxxiv, 81, 172, 263; ibid, xxxv, 119; Wheelon: Ibid., 1914, xxxv, 283; Hoskins: Ibid., 1915, xxxvi, 423; Hoskins and Rowley: Ibid., 1915, xxxvii, 471.

subsidiary center in the cord. From here it is relayed to an outgoing *preganglionic fiber* in one of the white *rami communicantes* of the sympathetic system. In one of the sympathetic ganglia it passes over to one or more *postganglionic* fibers, through which it finally reaches the arteriole wall. Between the terminal of this fiber and the smooth muscle cell proper on which the impulse acts is interposed a *myoneural junction*. This consists essentially of a "receptive substance" which bears to the muscle cell somewhat the same relation as does the percussion cap to the gunpowder of a loaded cartridge. Of the various constrictor centers that in the medulla is supposed to be of predominant importance. This is indicated by the fact that cutting the spinal cord just below the medulla usually causes a greater fall of blood pressure than does the further destruction of the cord itself.

This description takes account only of impulses which stimulate the vasoconstrictor mechanisms and cause a rise of pressure. By way of completeness it should be mentioned that other impulses cause a dilatation of the arterioles and a fall of pressure. The details in regard to the vasodilator mechanism are not at all well understood and for the purposes of this paper need not further be considered.

From the fact that curare changes the reflex irritability of the vasomotor system without a corresponding change of blood pressure level, Porter has recently concluded that there are both a vasoreflex center and a vasotonic center.[2]

The effects of hemorrhage on vasomotor irritability have been studied twice in recent years by American investigators. Porter[3] in 1907 and he, with Marks,[4] in 1908 published two papers on the subject. They were concerned mostly, however, in determining the extent to which blood pressure would have to be reduced before sensory nerve stimulation would cease to be effective in changing blood pressure. It was noted that as the general blood pressure fell a given stimulus produced a smaller absolute change of level than under normal conditions. Porter maintains, however, that the *absolute* change of level is not a proper criterion of vasomotor irritability. He illustrates the matter by an analogy:

> An unfaithful trustee robs two women. One of these has $40,000, the other $20,000. From each he takes $10,000. The absolute loss is the same, but while one woman can still live on her income the other must work or beg. It is necessary, then, in measuring vasomotor reflexes to take into account the level of the blood pressure at the beginning of stimulation, and this is done by expressing the change in blood pressure as a percentage of this level.

Judged by this principle the irritability of the vasomotor center is increased by hemorrhage, since the percentile rise of pressure on

2. Porter: Am. Jour. Physiol., 1915, xxvi, 418.
3. Porter: Am. Jour. Physiol., 1907, xx, 399.
4. Porter and Marks: Am. Jour. Physiol., 1908, xxi, 460.

stimulation is greater. Porter's analogy, however, is imperfect so far as hemorrhage is concerned. It assumes that the change in conditions during the experiment involves only the center. As a matter of fact, however, the conditions throughout the whole vasomotor mechanism are changed. We shall revert to this point in a later paragraph. Sollmann and Pilcher[5] on experimental grounds deny the validity of Porter's reasoning. They found in experiments involving pressure changes due to aortic compression that as a matter of fact the percentile rise varies *inversely* to the level of pressure. According to this finding Porter's and Marks' experiments would indicate a loss of vasomotor irritability during even the earlier stages of hemorrhage. Pilcher and Sollmann in a later study[6] have obtained results which are in direct contradiction to those just referred to. They report that any degree of hemorrhage lessens the pressor response to sciatic stimulation. This is true even when the general pressure level remains unaltered. In such a case there can be no question of "percentile change."

In view of the conflicting tenor of these late reports the matter seemed to us in need of further investigation, particularly as we were familiar with a somewhat different technic than that previously used. An obvious defect in the studies cited is that attention was fixed on the vasoconstrictor center without adequate regard to conditions in other parts of the apparatus.

Modern pharmacology, however, has afforded means of studying separately the condition of different parts of the vasomotor mechanism. This is done by injecting appropriate drugs which selectively stimulate these parts. The condition of the peripheral tissues can be tested by the use of epinephrin which stimulates the myoneural receptive substance, and, according to the best authorities, this only.[7] If there is any question as between the myoneural junction and the muscle cell proper, pituitary extract, which stimulates the cell only, can be used. The irritability of the motor cells in the vasoconstrictor centers and the outlying ganglia can be determined by nicotin, which, in proper dosage (0.2 mg.), selectively stimulates these.[8] Dosage in this connection, however, is of great importance. If large quantities are used a generalized stimulation of many structures occurs, followed shortly by a paralysis of the sympathetic ganglion cells. In this event

5. Sollmann and Pilcher: Am. Jour. Physiol., 1913, xxxi, 211.
6. Pilcher and Sollmann: Am. Jour. Physiol., 1914, xxxv, 65.
7. See, for instance, Pilcher and Sollmann: Jour. Pharm. and Exper. Therap., 1915, vi, 339.
8. Langley and Dickinson: Jour. Physiol., 1890, xi, 297. Pilcher and Sollmann: Jour. Pharm. and Exper. Therap., 1915, vi, 369.

vasomotor impulses are of course completely blocked. Both nicotin and epinephrin, and, to some extent, pituitary extract also, have the advantage that, in the dosages used, they can be repeated several times without significant loss of effectiveness. It is feasible, therefore, to study the changes of irritability of the vasomotor mechanism throughout the course of an experiment.

Using these methods the studies herein reported were carried out. While considerable individual variability was encountered, the essential concordance of the series as a whole permits a brief description of the results. The experiments were all made on unconscious subjects, dogs, either anesthetized with ether or decerebrated. Blood pressure from a femoral artery was recorded by means of an ordinary mercury manometer and float. The use of a Hall reservoir canula added materially to simplicity of technic. This is a glass canula of the ordinary arterial type in which is blown a 15 c.c. bulb (Fig. 2). The canula filled with 10 per cent. solution of sodium citrate can be connected by a rubber tube full of the same solution directly to the manometer. One charging of the bulb ordinarily suffices for two hours recording. There is no necessity, therefore, for the cumbersome "positive pressure" and "wash out" arrangements commonly used in such experiments. We have used the method only with dogs. Whether it would be satisfactory with smaller animals we have not ascertained. The rate at which the drugs are injected is an essential factor in quantitative experiments. In order to keep this constant, a flushing system was employed. A large bore cannula was fastened in a femoral vein. It was connected by rubber tubing to a reservoir of 0.8 per cent. sodium chlorid solution at an elevation of two feet. The tube was clamped near the end of the cannula. The drug to be given was injected by means of a hypodermic syringe into the tube immediately above the clamp. This was at once released and the drugs instantaneously sent into the blood stream. This technic reduces the margin of experimental error to neglible proportions. Better results are secured in the study of vasomotor reflexes by cutting the vagi and thereby eliminating secondary cardio-inhibitory reflexes. Nearly all our dogs were therefore vagotomized.

Fig. 2.—The Hall reservoir cannula, one-half size.

THE EFFECTS OF HEMORRHAGE

It was noted that after moderate hemorrhage the reaction to a given dose of nicotin was augmented, often to a striking degree. But the lower blood pressure that also resulted materially changed the mechanical conditions under which the vascular apparatus was working. The individual muscle cells had to contract with lower initial tension, from a shorter initial length and against a decreased load. The results were often correspondingly hard to interpret, although in certain instances the reaction was so greatly augmented as to be unequivocal. More satisfactory results were secured when, after the hemorrhage, enough isotonic saline solution was infused to restore the original pressure level and the reactions immediately determined.

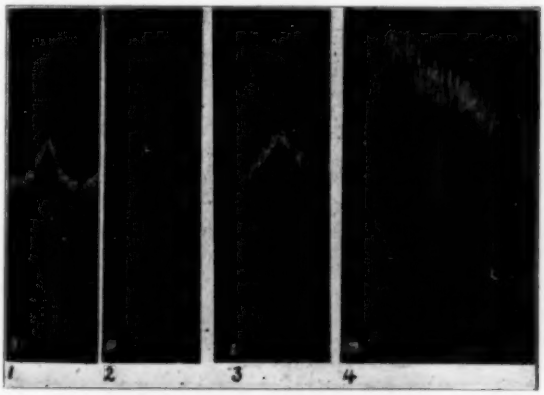


Fig. 3.—Effect of hemorrhage on vasomotor irritability. Blood pressure from femoral artery. Vagi cut. Graphs 1 and 2, reactions to 1 c.c. epinephrin (adrenalin), 1:100,000 before and after hemorrhage. Graphs 3 and 4 reactions to 1 c.c. nicotin 1:4,000 before and after hemorrhage (2 and 4 followed hemorrhage six to eight minutes). Hemorrhage 185 c.c. compensated with warm saline solution, 125 c.c. Dog weight, 11 kilos. Base line = 0 — pressure, signals and time (five seconds). Reduced to one-half.

The fluid was of course injected at body temperature. Figure 3 illustrates the outcome of such an experiment. Graphs 1 and 2 show the reactions to 1 c.c. of epinephrin (adrenalin) (1:100,000) before and after hemorrhage. They show that little change had occurred in the condition of the peripheral parts of the apparatus. Graphs 3 and 4 show the reactions to nicotin (1:4,000) also before and after the hemorrhage. The marked augmentation of the reaction shows that the irritability of the vasomotor nerve cells had been increased. Whether the change occurred in the vasoconstrictor center, however, or in the cells of the outlying *ganglia* can not from such an experiment be deter-

mined. It is probable that with the dosage used the rise of blood pressure is due largely to stimulation of the vasoconstrictor center proper, but no definite proof is available. No feasible way occurred to us to determine directly in these particular experiments which of the two sites was involved. It was supposed, however, that the essential feature of the experiments was an interference with the circulation in the medulla, leading to partial anemia of the center. Accordingly the experiments were extended as indicated in the next section.

### THE EFFECT OF OCCLUDING THE CAROTID ARTERIES

The medulla gets most of its blood supply from two sources, the carotid and the vertebral arteries. While clamping the carotids leaves the medullary centers enough circulation to permit their functioning,

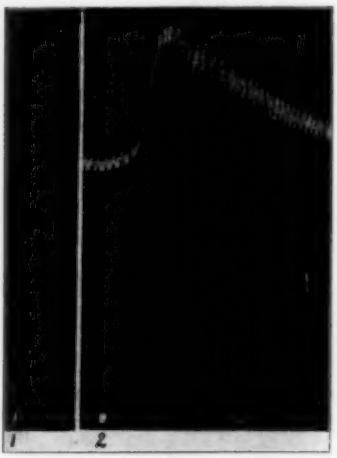


Fig. 4.—Effect of occluding carotid arteries on vasomotor irritability. Blood pressure from femoral artery. Vagi cut. Graph 1, reaction to nicotin, 1 c.c. 1:4,000 before occlusion. Graph 2, reaction to same dose five minutes after occlusion. Base line = 0 — pressure, signals and time (five seconds). Reduce to one-half.

it was thought that a sufficient degree of anemia might be caused to produce an appreciable effect. In nearly every instance the procedure actually did cause a marked change in the reaction to nicotin. Figure 4 illustrates one of the more marked cases. Graph 1 shows the reaction of 1 c.c. of nicotin (1:4,000). Both carotids were then clamped. The pressure level rose to the height shown in Graph 2. Five minutes after the occlusion the same dose of nicotin now caused the much greater rise shown in Graph 2. The reactions to epinephrin were prac-

tically the same in both cases. The essential difference, therefore, in the conditions before and after occlusion is an augmented irritability of the vasoconstrictor center. The augmentation in reaction is all the more striking because the occlusion must have partially protected the medulla from the inflow of nicotin. In the few instances in which little augmentation occurred the vertebral arteries probably were adequate to keep up a full blood supply. In one such case pressure on one vertebral artery in addition brought out the augmentation phenomenon. The concordance of both the hemorrhage and occlusion experiments indicates that the augmented irritability was in the vasoconstrictor center proper and not in the outlying ganglia. A characteristic feature of both the hemorrhage and the occlusion experiments was an increase in the length of time the pressor reaction continued.

The occlusion experiments are in harmony with clinical observations. Elevation of blood pressure is one of the accepted signs of increased intracranial pressure following contusions of the brain. But the clinical observations do not, in themselves, show whether the elevated pressure is due to increased irritability of the vasoconstrictor center or to increased stimulation of the center, perhaps by asphyxial products, or to both. The two conditions are allied but by no means identical. That irritability can be greatly augmented without concomitant stimulation is well known to any one familiar with the pharmacology of strychnin. Parenthetically it might be added that "pressure on the medulla" can not, as such, account for the raised blood pressure following brain edema. Slowly developing pressure does not stimulate but depresses.

The underlying feature in all these cases is probably an increase in the hydrogen ions in the cells concerned. Anything which interferes with the circulation of a tissue tends to cause an accumulation of acid products, such as carbon dioxid and lactic acid. This, for example, is probably the essential element in the so-called "hyperemia" treatment (Bier's), which amounts to partial asphyxia and an attendant increase of local tissue activity. A somewhat similar phenomenon is seen in the familiar process of "warming up" of athletes, or, in its laboratory guise, the "stair-case" phenomenon. In each case the efficiency of the mechanism is improved by use. The conventional explanation is that the activity liberates acid products which augment the irritability of the tissues.[9]

The augmented irritability of the vasoconstrictor center described in this paper would seem to have some significance as an adaptive arrangement. Several factors are recognized as aiding in compensation after hemorrhage. Such are the characteristic rapid

9. Lee: Am. Jour. Physiol., 1907, xx, p. 170.

heart beat, the passive contraction of the vascular channels due to the inherent elasticity of the vessel walls, and the withdrawal of fluids from the tissue to restore the volume of the circulatory medium. Augmented vasoconstrictor irritability leading to higher vasomotor tonus would cooperate with these other factors in maintaining pressure and keeping up circulation in the brain at the expense of outlying tissues. Similarly when the circulation in the brain is impeded by intracranial pressure the augmented vasomotor tonus by raising systemic pressure aids in keeping the vital centers supplied. This significance of hypertension is of course well recognized.

In this paper only moderate degrees of hemorrhage have been considered (10 to 20 c.c. per kilo of body weight). As is well known, more extensive loss of blood or serious arrest of its circulation from any cause quickly induces a marked depression of the whole central nervous system. In this depression the vasoconstrictor center of course shares.

## SUMMARY AND CONCLUSIONS

1. Certain drugs selectively stimulate different components of the vasomotor apparatus. It is possible by their use to detect changes of irritability in these components.

2. Hemorrhage causes a marked augmentation of the reaction to nicotin but slight or no augmentation of the reaction to epinephrin.

3. Occluding the carotids in most instances leads to similar results.

4. The augmented reactions are probably due, therefore, to increased irritability of the vasoconstrictor center.

5. The phenomenon is probably an adaptive arrangement tending to preserve normal circulatory conditions.

# STUDIES IN DIPHTHEROIDS

## III. BACTERIA ISOLATED FROM ENLARGED GLANDS, ESPECIALLY IN HODGKIN'S DISEASE *

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The object of this paper is to put on record observations on bacteriologic studies in adenopathies, especially Hodgkin's disease, in the light of the findings of Fraenkel, Much, de Negri, Mieremet, Rosenow, Bunting and others.

The descriptions given in literature of bacteria isolated from malignant lymphatic granulomas seem to indicate a considerable difference in character among the isolated strains. Early in my work on Hodgkin's disease, it became evident that while diphtheroids might be isolated from many cases of this disease, and indeed from other adenopathies, they varied in morphology and biology. Cultures were sent me by Dr. E. C. Rosenow of Chicago (marked R) and by Dr. J. A. Kolmer (marked K), and comparison of these two sets with those obtained at the Pepper Laboratory showed that the impression stated above was correct. It seemed well to tabulate all the diphtheroids at my command to see if any one form were common in pathologic or clinical Hodgkin's disease or in other adenopathies, and to compare their biology with related organisms. Previous studies with this group have shown the great variations in the biology of morphologically similar diphtheroids, and I did not look for much assistance from this side. Judging from de Negri and Mieremet's work, it seemed that Bordet medium and the morphology, especially in connection with Gram's stain, would enable one to define with some degree of certainty the organism to be considered most important in Hodgkin's disease.

It might be well at this point to state that as Hodgkin's disease I have considered cases with more or less generalized progressive glandular enlargement in which the individual members of the group did not fuse and soften, and showing under the microscope diffuse, mononuclear hyperplasia, prominence of large endothelioid cells and eosinophils, which elements are separated irregularly by a fine fibrosis. These glands should also show small necroses. This description is based on the disease picture as outlined in the work of Reed and

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* From the William Pepper Clinical Laboratory, University of Pennsylvania.

Longcope. Search has always been made for tubercles and tubercle bacilli. The microscopic anatomy of Hodgkin's disease is by no means constant, and I doubt if the borderline between it and that of chronic adenitis and tuberculosis is clear in any one's mind. In citing my own cases below, the name "Hodgkin's disease" has been used only as a clinical term, pathologic diagnosis being made on the anatomic findings. The material for these studies was obtained by operation under local anesthesia or gas. In the arthritis cases, the most accessible gland or that near the principal joint focus was removed. Free glands of moderate size and firmness were selected from the Hodgkin's cases.

The following is the method used in studying the cases:

A section of a gland removed at operation was cut at once, one piece put into Orth's fluid or liquor formaldehydi, another dropped into hot oil, transferred to ether, then into salt solution and from that into a large sterile bottle; cut up with scissors within the bottle, pieces removed and planted on Bordet medium tubes and plates, serum dextrose agar, Loeffler's blood serum, serum water and rabbit blood agar. Smears made from a bit of the gland stained with Loeffler's, Gram's, carbolfuchsin and Wright's. In most of the cases the bits of tissue remaining after inoculating sufficient culture mediums were put into 15 per cent. antiformin, incubated at 37 C. over night and seeded on the same mediums. Two of the cases were fortunately exposed to antiformin only for an hour because cultures were positive then and negative after eighteen hours' exposure. All the cultures were plated on Bordet medium except two early ones before the necessity of this procedure was appreciated. It is necessary in this work to be sure that one has pure cultures. It is best to plate on Bordet medium and fish after three days' incubation, at which time the slightly varying colonies are differentiated. This medium has a good contrast surface.

The accompanying table was compiled from records made on cultures growing on mediums of the same method of preparation, and the cultures from Drs. Rosenow and Kolmer were tested on the same batch of mediums and at the same time, as Nos. 8772, 8916, 9144, 9265 and 9392, while the control, true diphtheria bacilli and pseudo forms 873-1 and 873-3 were grown on the same batch of culture material as 6638 and 6640. Observations on carbohydrates were made on litmus agar sugar mediums of reaction neutral to phenolphthalein. The other standard mediums were of 1+ reaction. Cultures isolated in the Pepper Laboratory are given numbers, while those from Drs. Rosenow and Kolmer are lettered. The generations from which these notes were made varied from the third to the tenth. Nos. 8772, 8916, 9265, 7144, 9392, the R's and the K's were all passed through three times and remained uniform in biology. The morphology has not been controlled by repetition to the same extent, but comparison of the original smears and those made during the cultural observations indicate that the staining characters remain the same. Culture 8772, now in its thirty-third generation, is the only one to change materially, having lost its beaded and segmented character and staining as long, slender, solid

rods. The drawings were made by the same person with the same equipment throughout.

CASE 1 (6638).—A. S., a woman, aged 22, three months ago noticed that her neck began to swell on the left side, giving her no discomfort or pain. About two weeks later she noticed the same condition on the right side. One month later she noticed that she had lumps in the right axilla. There never was any pain or discomfort in these swollen glands. The glands on both sides of the neck have been steadily increasing in size; the most rapid growth shows in the glands in the right axilla.

Physical examination reveals a large mass of glands in the anterior of the neck on both sides. On the right the nodules are more discrete, although a number of them are massed together, on the left side they are at places definitely outlined, but the majority of the mass of glands are adherent. They are all very hard, smooth and noninflammatory, and in places are fixed quite tight. In the right axilla are a number of glands, one about the size of an egg, which is hard, smooth and discrete. It is also noninflammatory. Blood: R. B. C., 3,350,000; W. B. C., 14,200; Hb., 53 per cent.; P., 81 per cent.; L., 14 per cent.; M., 3 per cent.; T., 2 per cent.; E., 0 per cent. The axillary gland was removed under local anesthesia.

Section shows chronic lymph granuloma with an attempt to preserve lymphoid collections, but these and the chords are encroached on by diffuse round cell and endothelial leukocyte infiltrates and fine fibrosis. Eosinophils and multinucleated cells are numerous. Connective tissue is everywhere increased and hyaline. The focal necroses are missing; growth is active, as indicated by normal mitosis and many compression giant cells. Diagnosis, lymph granuloma.

CASE 2 (6640).—L. P., aged 30. The patient first noticed a swelling in the right side of the neck one year ago. Twelve weeks ago cough and vomiting were present, eight weeks ago, fever, pain in abdomen, and sweating occurred.

Physical examination showed the lymphatic glands of the neck, axilla and right inguinal region to be greatly enlarged; the greatest enlargement was in the right cervical chains; here some were the size of small lemons; they extended from the angle of the jaw to the clavicle. There was one large one in the right submaxillary region. The enlargement was not so marked on the left; in the axillae they were about the size of horse chestnuts; they were not so large in the right groin; small ones were found in the left groin. No glands were palpable in the popliteal space or in the epitrochlear region. The glands were soft, movable, discrete and unattached to the skin; not tender. The chest showed pleural effusion; the abdomen, ascites, palpable liver and palpable spleen. Blood: Hb., 40 per cent.; R. B. C., 3,290,000; W. B. C., 4,100. Von Pirquet negative. Urine: Albumin and casts.

Section shows a tissue made up of large lymphocytes or endothelioid cells with a ground work of fine fibrosis and many scattered polynuclear cells. Eosinophils are numerous. There are many areas of necrosis, some wholly hyaline, others with a core of chromatin débris surrounded by a hyaline necrosis. Giant cells and multinucleated cells are numerous, most of which seem to be compression giant cells.

CASE 3 (8916).—W. P. Two years ago the glands on the left side of neck began to swell, followed shortly by the left submaxillary gland. Previous to this for some time he had had enlarged glands or kernels in his neck, especially over the left mastoid. About a year ago a playmate of the patient died of Hodgkin's disease, which started in a similar manner to that of the patient. The blood count showed: Hb., 85 per cent.; R. B. C., 4,330,000; W. B. C., 8,300; Diff.; P., 15 per cent.; L., 38½ per cent.; L. M., 41 per cent.; E., 4 per cent.; B., 1 per cent. The group of large mononuclears here includes large lymphocytes and myeloblasts, large mononuclears and transitionals.

## ILLUSTRATING FIGURES 1-4

Fig. 1.—1, 6638*a*, 48 hours agar—Loeffler; 2, 6638*a*, 48 hours Bordet—Loeffler; 3, 6638*b*, 48 hours agar—Loeffler; 4, 6638*b*, 48 hours Bordet—Loeffler; 5, 6640, 48 hours agar—Loeffler; 6, 6640, 48 hours Bordet—Loeffler; 7, 8916-1, 72 hours agar—Loeffler; 8, 8916-1, 72 hours Bordet—Loeffler; 9, 8916-1, 72 hours blood serum—Loeffler; 10, 8916-1, 72 hours agar—Gram; 11, 8916-2, 48 hours agar—Loeffler; 12, 8916-2, 48 hours blood serum—Loeffler; 13, 8916-2, 24 hours agar—Gram; 14, 8916-2, 24 hours Bordet—Gram; 15, 8916-4, 48 hours agar—Loeffler.

Fig. 2.—16, 8916-4, 48 hours Bordet—Loeffler; 17, 8916-4, 48 hours blood serum—Loeffler; 18, 8916-7, 48 hours agar—Loeffler; 19, 8916-7, 48 hours Bordet—Loeffler; 20, 8916-7, 48 hours bouillon—Loeffler; 21, 8916-9, 72 hours bouillon—Loeffler; 22, 8916-9, 72 hours Bordet—Gram; 23, 8916-10, 72 hours Bordet—Gram; 24, 9265, 48 hours blood serum—Gram; 25, 8772, 48 hours agar—Loeffler; 26, 8772, 72 hours blood serum—Loeffler; 27, 8772, 48 hours agar—Loeffler; 28, 8772, 72 hours Bordet—Gram; 29, 8772, 72 hours blood serum—Gram; 30, 9144-1, 48 hours Bordet—Gram.

Fig. 3.—31, 9144-2, 48 hours blood serum—Gram; 32, 9392-1, 48 hours agar—Loeffler; 33, 9392-1, 48 hours Bordet—Loeffler; 34, 9392-1, eighth day Bordet—Loeffler; 35, 9392-1, 72 hours Bordet—Gram; 36, R. A.-1, 48 hours Bordet—Loeffler; 37, R. A.-2, 48 hours Bordet—Loeffler; 38, R. B.-1, 48 hours Bordet—Gram; 39, R. B.-2, 48 hours Bordet—Loeffler; 40, R. B.-2, 72 hours Bordet—Gram; 41, R. B.-4, 24 hours agar—Loeffler; 42, R. B.-4, 48 hours Bordet—Loeffler; 43, R. B.-4, 48 hours Bordet—Gram; 44, R. C.-2, 24 hours agar—Gram; 45, R. C.-3, 24 hours agar—Gram.

Fig. 4.—46, R. C.-3, 24 hours Bordet—Gram; 47, R. C.-3, eighth day blood serum—Gram; 48, R. D.-1, 48 hours bouillon—Loeffler; 49, R. D.-2, eighth day agar—Gram; 50, R. E.-1, 72 hours Bordet—Loeffler; 51, R. E.-1, eighth day agar—Gram; 52, K. I.-1, 72 hours blood serum—Loeffler; 53, K. II.-1, 48 hours Bordet—Gram; 54, K. II.-3, 72 hours Bordet—Gram; 55, K. II.-4, 48 hours Bordet—Gram; 56, Klebs-Loeffler "K," 48 hours agar—Loeffler; 57, Klebs-Loeffler "K," 48 hours Bordet-Loeffler; 58, Klebs-Loeffler "K," 24 hours blood serum—Loeffler; 59, 873-1, Pseudo-diphtheria 48 hours Bordet—Loeffler; 60, 873-3, Pseudo-diphtheria 48 hours Bordet—Loeffler.

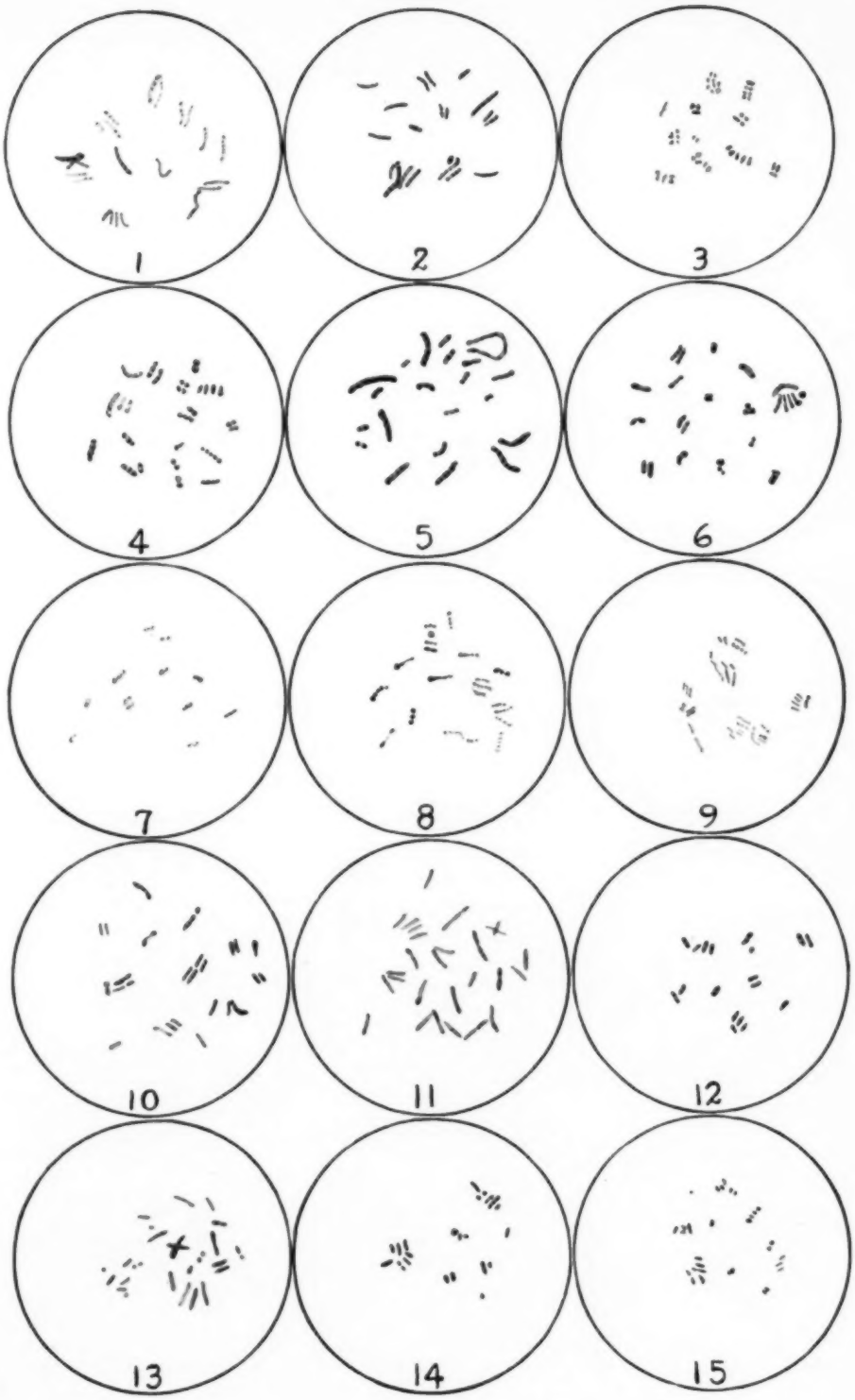


Figure 1

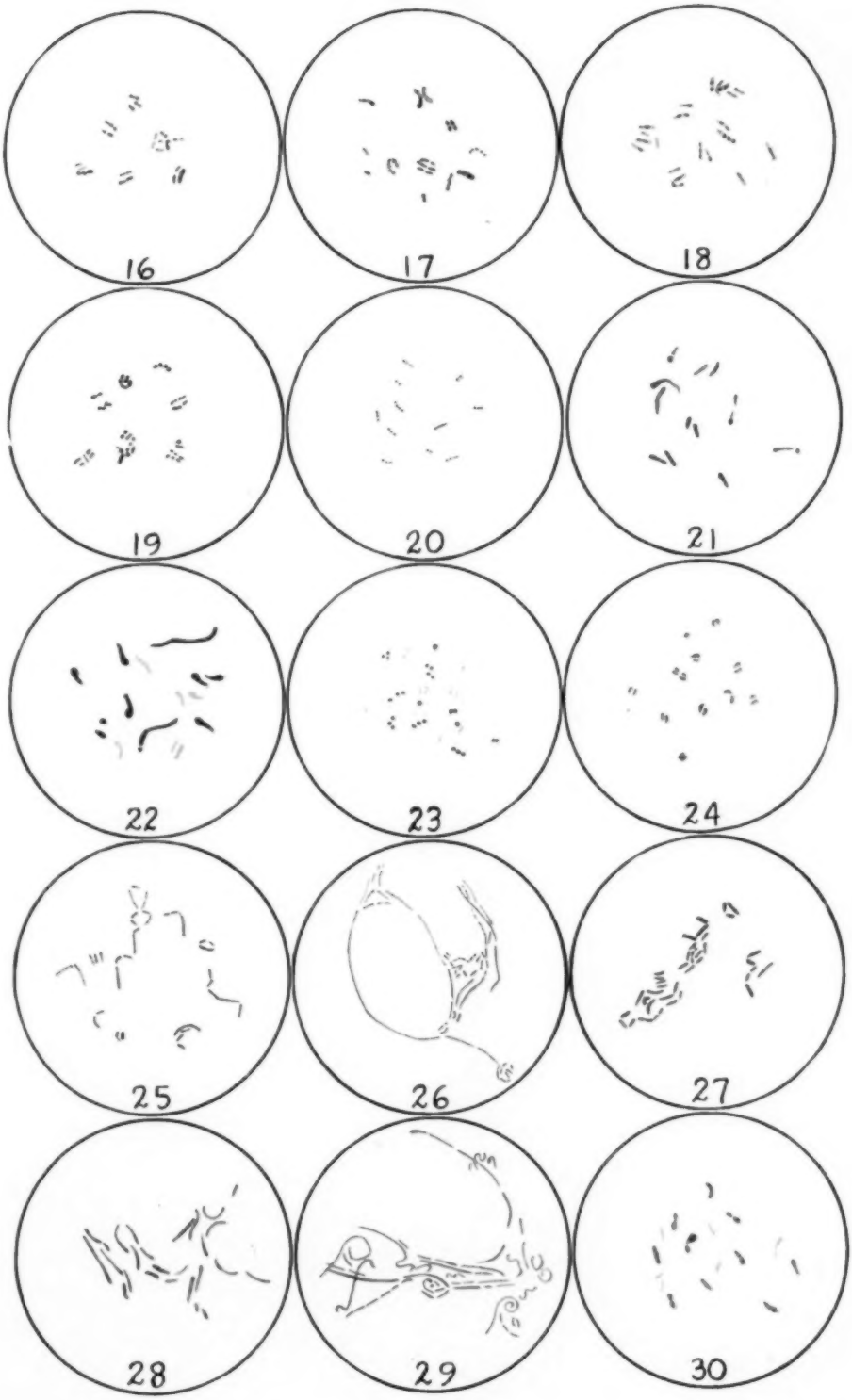


Figure 2

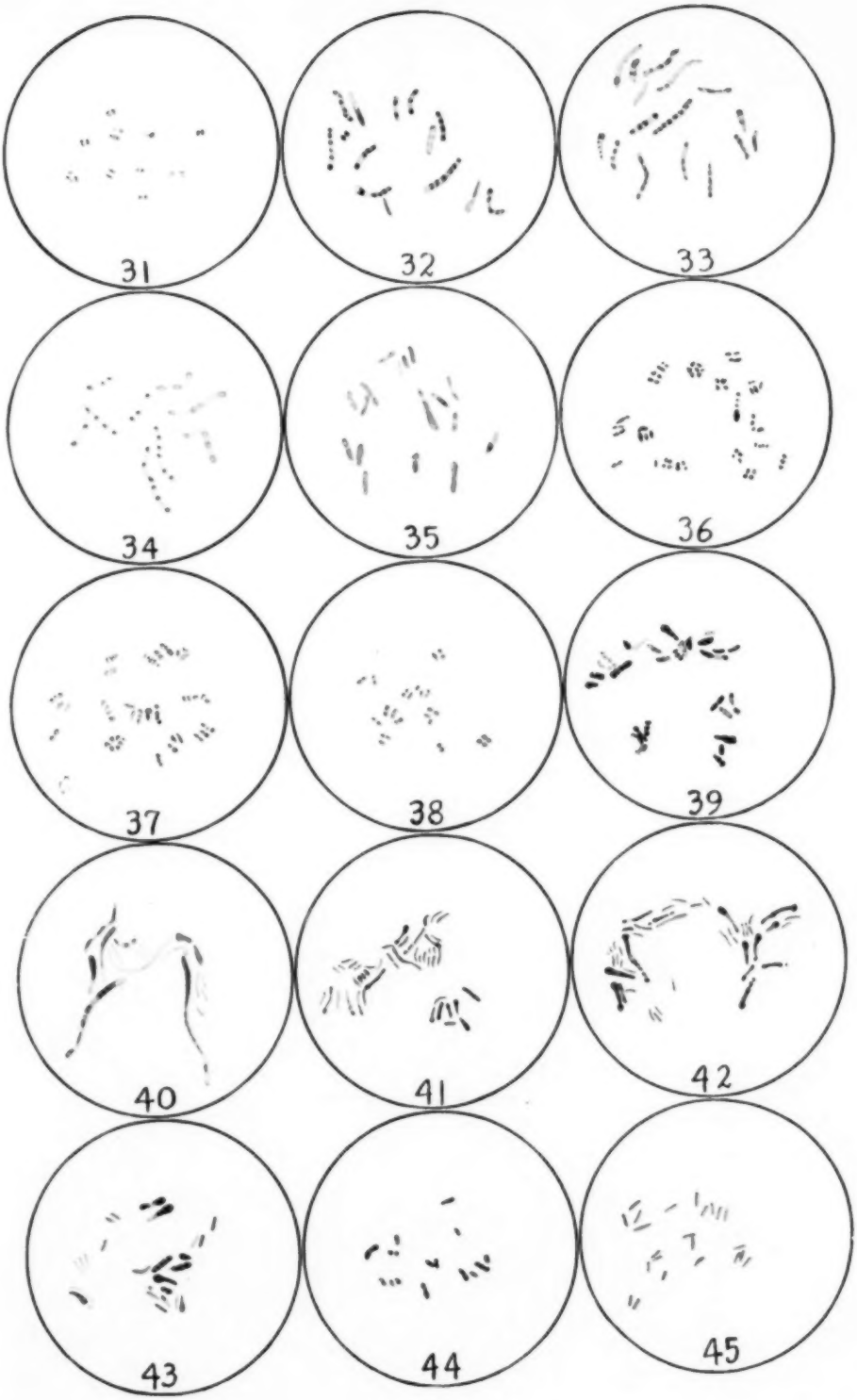


Figure 3

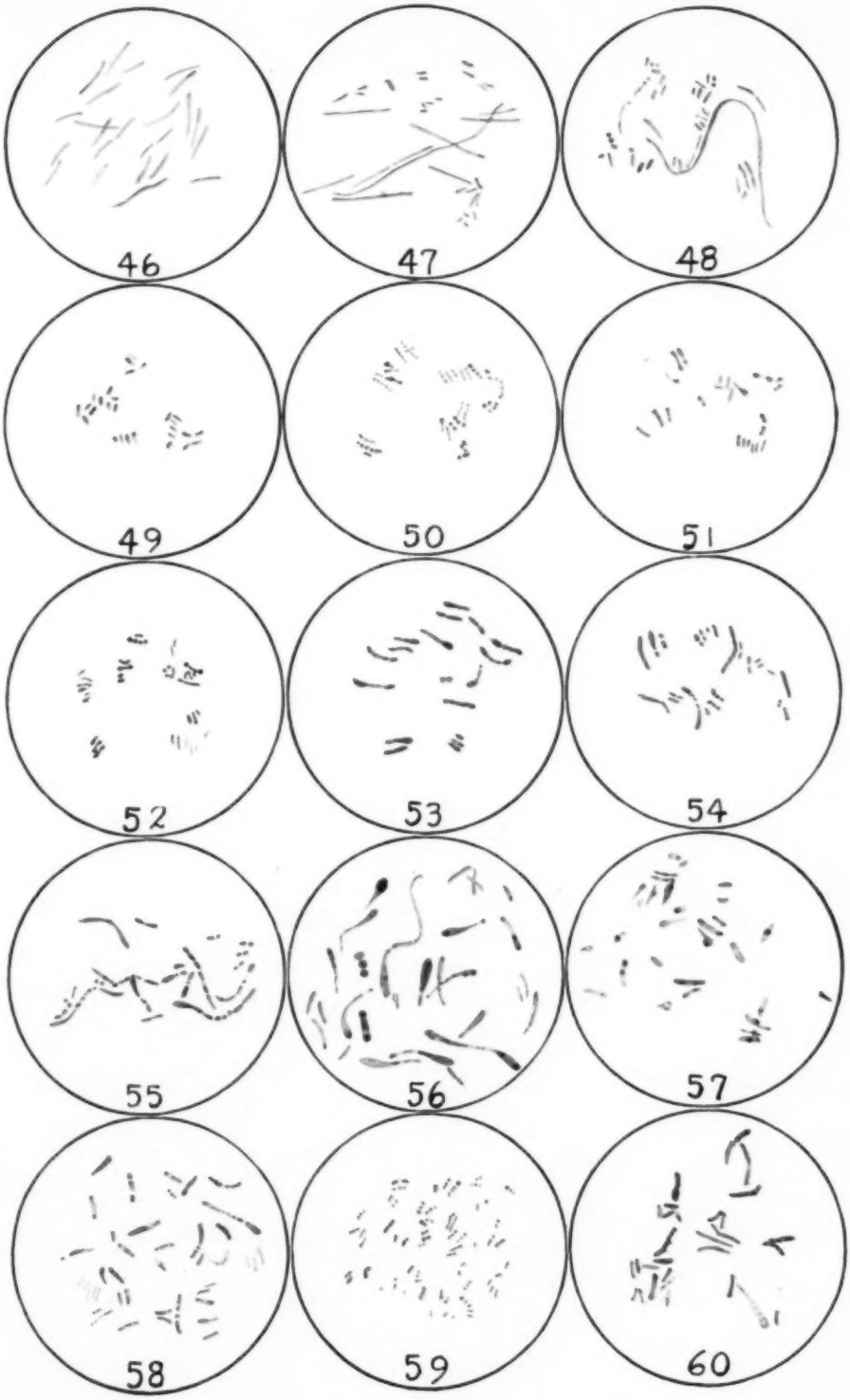


Figure 4

Physical examination showed the patient to be sallow or ashy. His neck was thin and suggested loss of weight. Considerable swelling was present in the left side of the neck involving the glands below the angle of the jaw and cervical region and postoccipital; but numerous small glands could be felt on both sides of the neck from the clavicle upward. There was doubtful enlargements in the right axilla, none in left. The inguinal glands were more distinct. A possible slight dulness was noted at the root of the right lung and harshness of inspiration. The sounds, however, were not altogether certain. The spleen was doubtfully palpable. No abdominal masses were noted.

Nov. 4, 1913: Marked improvement has appeared in the condition of the glands. Those of the neck have almost disappeared; one is still palpable just above the clavicle; none are discoverable in the axilla.

March 21, 1914: Some enlargement of the cervical glands still exists; these seem to be variable in size. A little while ago the patient noticed an enlarged gland in the right forearm or epitrochlear region, but this has disappeared.

March 28, 1914: Blood examination to-day shows a little improvement in hemoglobin and red cell count. Two series of Roentgen ray treatments have resulted in considerable improvement.

A gland about 5 by 4 mm. over the tip of the mastoid was removed under local anesthesia. The smears failed to show any rods. A section showed fairly well-encapsulated tissue of the general outline of a lymph node consisting of a disturbed follicular border and a medulla composed chiefly of fibrous tissue containing many dilated blood channels whose walls are imperfect and the endothelium of which is scanty. The follicular border shows loosely arranged lymphoid cells between which are red blood cells, and in the larger hyperplastic follicles, cells of the large mononuclear series. The endothelium of sinuses cannot be said to be increased. There are practically no eosinophils. There are no large phagocytes, no giant or ring cells. Here and there a fair number of polynuclears may be seen. The connective tissue of the medulla is well formed. The fibrils are clear and there seems to be no degenerative change in the section anywhere. It seems more like a chronic lymphadenitis than Hodgkin's disease or tumor.

The patient was continued on Roentgen ray and vaccine treatment and improvement has continued.

CASE 4 (9265).—E. P., aged 24, colored, has had general adenopathy and rheumatic pains throughout the joints and extremities, for only about four weeks. The gland remained firm and discrete and the case seemed one of Hodgkin's disease. Histologic section showed chronic follicular enlargement with moderate intrafollicular and perifollicular fibrosis, compression of sinuses almost to obliteration, a notable increase in large mononuclears and fibroblasts of chords. Eosinophils and necrosis are absent; there was no tubercle formation, no giant cells. Cultivation produced a large micrococcus in pairs, each individual having a long transverse diameter but no rods. The patient refused to stay in the hospital and was lost to further observation.

CASE 5 (3541).—McC., had adenopathy of both cervical and right axillary regions which began as an enlargement of the right epitrochlear gland. The right pectoral region was indurated like carcinoma *en cuirasse*. After removal of some glands for experimental purposes, the patient developed a general pneumococcus infection and died.

Section from operated glands showed a chronic adenitis with features of sarcoma, in places very like endothelioma. The cultures remained sterile except one Bordet medium tube and one blood agar tube and one blood serum tube on which grew a white coccus. No colonies of rods could be discovered.

Necropsy showed a sarcomatous growth of the lymph glands, probably endothelioma. As the cell was small, round or oblong with a small amount of acid-staining protoplasm and a large vesicular and hyperchromatic nucleus, the tumor possibly arose from the endothelial cells of the lymph spaces. The rest

of the postmortem indicated arteriosclerosis, fibrosis in the lung and the evidences were found of the acute infection through which the patient had passed.

CASE 6 (8772).—L. W., a woman, aged 32, had bilateral cervical adenopathy of four months' duration with firm, discrete glands. At operation those removed showed a yellow-gray surface with a few minute points of hemorrhage. Near the margins there was apparently fine fibrosis. The gland section was dry. Microscopic examination revealed a rapidly growing lesion chiefly along the lymph channels, made up of large, palely staining, irregular cells; probably endothelioma. The fibrous tissue was abundant, but loose. There was no resemblance to Hodgkin's disease. Culture on Bordet and blood agar gave some colonies of cocci and one brownish colony on a Bordet tube, proving to be an irregular granular rod.

Roentgen ray and vaccine treatment was instituted with at first favorable results. The patient was pregnant on arrival at the hospital, and it was decided that termination of this condition was necessary for her good. After return from the maternity, treatment for the adenopathy was resumed. The patient left the hospital in a short time. The report is that she has died.

CASE 7 (8604).—J., aged 19, had bilateral adenopathy with an acute exacerbation since the removal of adenoids and tonsils two months before operation. Large masses of discrete glands were found, the individual glands being soft and resilient. Operation showed soft, fatty, necrotic, gray-yellow glands with here and there precaseous necrosis. Caseous tuberculosis was confirmed by stain and section. *M. albus* appeared in pure culture in every tube. No diphtheroids were noted.

CASE 8.—A. G. F., a woman, aged 33, was in good health until seven years ago, when she became pregnant and at the same time developed a swelling in the right side of the neck which lasted two months and then disappeared. After the birth of her child, a similar swelling developed in the right axilla which remained until five years ago when it was drained, at which time it was very much inflamed and contained pus. Two years ago glands were removed from the neck and axilla.

Smears and cultures made in the ordinary way showed no tubercle bacilli, two slender, solidly staining rods and one pair of cocci by Loeffler's stain. The small lymphocytes, large mononuclears and a few polynuclears were most numerous. Incubation of the gland on Bordet and blood agar for six days showed nothing. A section from the gland showed a disturbed follicular border, between the lymph-cell collections of which are irregular areas of epithelioid cells and an occasional giant cell. The margins of the epithelioid cell collections showed numerous fibroblasts toward the center of the gland. Areas of eosin-staining necrosis are present. No eosinophils are to be seen. A few tubercle bacilli may be noted.

CASE 9 (9144).—M. W., a white woman, aged 22, had always been healthy until four months before admission, when she had an attack of tonsillitis lasting one week. Following this her left wrist became swollen, red, hot, tender and stiff, and later her left ankle, right wrist, knees, elbows and shoulders became involved in a similar manner. Finally the finger joints were involved and these were at the time of admission, giving her the most trouble. In the meantime she had been given twenty-four antirheumatic antitoxin injections without benefit, and, indeed, had lost 18 pounds in weight.

Physical examination showed a somewhat sallow complexion; a gland the size of a finger tip was palpable in the right axilla, and a few posterior and anterior cervical nodes were palpable. The tonsils and pharynx were somewhat congested. There were sordes on the teeth and a slight pyorrhea was present. The elbows were fixed in partial flexion, the wrists limited in motion. The proximal phalangeal joints of both hands were swollen, slightly reddened, hot and tender; these swellings were fusiform in shape. The power in the hands was decidedly diminished. The gonococcus fixation test and Wassermann were

negative. Roentgenoscopy of the hands showed beginning atrophic arthritis of the proximal phalangeal joints. May 21, Dr. Eliason removed a gland from the right axilla for culture and microscopic examination. On discharge she was greatly improved; the elbows were movable, the swelling of ankles and wrists had diminished, the power in the hands had increased.

A smear failed to show any bacteria. Cytology was negative. A section shows large loose follicles with quite definite increase in delicate connective tissue. The interfollicular sinus architecture is disturbed by the growth of the follicles, and fibrous tissue is definitely increased. The capsule is little, if any thickened. No especial kind of cell other than the small lymphoids is present. There is no necrosis, no eosinophils.

CASE 10 (9392).—J. M., a woman, aged 41. Her present illness began seven years ago, coming on a few hours after delivery with pain and tenderness in spine; soon other joints were involved—knees, shoulders, elbows, wrists and fingers. Trouble then varied from time to time, never very severe, until two months ago, when she had an acute exacerbation in the knees, both becoming red and swollen.

Physical examination showed the right epitrochlear to be the only gland palpable. The tonsils were atrophic. The right shoulder and elbow were tender and motion was limited. Atrophic changes appeared in the finger joints. There was marked swelling of both knees, the right one being the larger and somewhat tender, and presented a distinct fluctuation. Roentgenoscopy of the wrist showed atrophic changes. Cultures from the throat were negative; from the fluid from the knee joint also negative; from the blood, negative. The right epitrochlear gland was removed and three organisms isolated. Autogenous vaccine was started. On discharge after only three injections, she was feeling much better, the anemia was improving and the pain in the knees had decreased and was entirely absent in the other joints.

CASE 11 (4554).—G. P. Three years ago, following an attack of grip with tonsillitis, the patient developed acute arthritis in the small joints of the feet; later in the wrists and fingers. These early attacks were associated with chills and acid sweats. Deformity persisted and has gradually progressed. The patient has lost weight and there has been considerable atrophy and progressive weakness of the muscles of the upper extremities. There is at present involvement of the fingers, elbows, wrists and knees, the most active process being in the knees. The tonsils are small but diseased, no other focus of infection being discoverable. October 16, a small lymph node was removed from the right groin for culture with negative result. Section shows a mild chronic lymphadenitis.

CASE 12 (4555).—J. E., two years ago, developed acute arthritis in the right wrist, gradually progressive; since then the process has extended to the elbows, both wrists, fingers and knees, and includes the temporomandibular joints. No focus of infection has been found. Repeated blood cultures have been sterile. The most active joints at present are the knees. October 15, a small lymph node was removed from the left groin for culture. Result was negative.

CASE 13 (5639).—B. N., aged 40, white. Present illness began two weeks ago with pain in back, spreading to hands and knees, these joints becoming swollen. Then, in order, hips, ankles, shoulders and elbows were involved. At first the trouble went from one joint to another. Now all are involved.

Physical examination shows irregularity of pupils, pyorrhea, cervical adenopathy. The heart is negative. Both shoulders are limited in motion and crepitate. The left elbow is ankylosed and tender. The left wrist is tender, enlarged, motion limited. All finger joints are similarly affected. There is muscular wasting about the joints of the upper extremity. The right knee-joint is enlarged and tender. There is some effusion and motion is limited and associated with muscular atrophy. The ankle and toes are likewise affected. Von

| Case No. | Age and Sex | Duration | Clinical Diagnosis | Pathologic Diagnosis | Vaccine Therapy and Result | Forms of Bacteria Found | Acid and Antiformin Fast | Agar | Blood Agar | Blood Serum | Bordet |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6638 a A. S. | 22 ♀ | 3 mos. | Hodgkin's disease | Lymph granuloma of endothelioid type, fibrosis, necroses and eosinophils | Improved ? | Diphtheroids | 0 Antiformin fast | Dull gray, flat band of discrete delicate colonies | As agar becoming opaque | As agar but glistening and confluent | As agar becoming confluent, spreading and brown |
| 6638 b | 22 ♀ | 3 mos. | Hodgkin's disease | Lymph granuloma of endothelioid type, fibrosis, necroses and eosinophils | Improved ? | Diphtheroids | 0 Antiformin fast | Glistening, raised, yellow-white, smooth, entire band | As agar pinkish; hemolysis slight | As agar | Slightly waxy, flat, dirty gray - green band becoming brownish, medium brown-yellow, then greenish-brown |
| 6638 c | 22 ♀ | 3 mos. | Hodgkin's disease | Lymph granuloma of endothelioid type, fibrosis, necroses and eosinophils | Improved ? | Diphtheroids | 0 Antiformin fast | Luxuriant, opaque, glistening, white, entire band | As agar more luxuriant; hemolysis + medium becomes brown-opaque | As agar more luxuriant | Dirty gray, raised, dull band with glistening edges, becoming brown, medium first, yellow-brown then green |
| 6640 L. P. | 30 ♀ | 1 yr. | Hodgkin's disease | Lymph granuloma of endothelioid and mononuclear type, fibrosis and eosinophilia | Yes, Improved ? | Diphtheroids Three slightly varying colonies with same morphology and biology | Antiformin fast (?) 1 hour + 18 hours 0 | Delicate, dull, moist, translucent, dirty-white band | As agar hemolysis 0 | As agar more luxuriant | Thin, moist, gray band |
| 8916-1 W. P. | 9 ♂ | 7 mos. | Hodgkin's disease | Lymphadenoma of chronic hyperplastic variety | Improvement with Roentgen ray, later bacterins added greater improvement | Seven closely similar diphtheroids. M. albus | 0 Rods not destroyed but not acid-fast | Moist, flat, yellow, entire, discrete | Slimy, dirty-white, opaque | Faint orange-yellow, discrete, sunken colonies, liquefaction + | Slimy, moist, opaque, luxuriant, yellow becoming greenish |
| 8916-2 | 9 ♂ | 7 mos. | Hodgkin's disease | Lymphadenoma of chronic hyperplastic variety | Improvement with Roentgen ray, later bacterins added greater improvement | Seven closely similar diphtheroids. M. albus | 0 Rods not destroyed but not acid-fast | Delicate, flat, colorless streak | Delicate, flat, discrete colonies | Flat, even, delicate streak, becoming yellow | Glistening, moist, pale gray, spreading, becoming brown, medium chocolate |
| 8916-4 | 9 ♂ | 7 mos. | Hodgkin's disease | Lymphadenoma of chronic hyperplastic variety | Improvement with Roentgen ray, later bacterins added greater improvement | Seven closely similar diphtheroids. M. albus | 0 Rods not destroyed but not acid-fast | Faint, moist, glistening band becoming yellow, then gray | As agar, but becoming brownish-gray | Faint, dry, white band | Luxuriant, dull orange-yellow, becoming gray, flat and dry |
| 8916-7 | 9 ♂ | 7 mos. | Hodgkin's disease | Lymphadenoma of chronic hyperplastic variety | Improvement with Roentgen ray, later bacterins added greater improvement | Seven closely similar diphtheroids. M. albus | 0 Rods not destroyed but not acid-fast | Faint, dull, yellow-white band | Dull, yellow-white butyrous | Faint, dull-yellow, and dry brown | Thin, dull, flat, brown-yellow, becoming frosted gray |
| 8916-8 | 9 ♂ | 7 mos. | Hodgkin's disease | Lymphadenoma of chronic hyperplastic variety | Improvement with Roentgen ray, later bacterins added greater improvement | Seven closely similar diphtheroids. M. albus | 0 Rods not destroyed but not acid-fast | Glistening, moist, raised, yellow, becoming brownish | As agar | Slimy, yellow, depressed; liquefaction = + | Smooth, flat, limited, waxy, pale brown |
| 8916-9 | 9 ♂ | 7 mos. | Hodgkin's disease | Lymphadenoma of chronic hyperplastic variety | Improvement with Roentgen ray, later bacterins added greater improvement | Seven closely similar diphtheroids. M. albus | 0 Rods not destroyed but not acid-fast | Flat, moist, slimy, pale yellow | As agar but becoming brownish | Flat, smooth, glistening, lemon-yellow | Like agar but more luxuriant; distinct brown, chocolate |
| 8916-10 | 9 ♂ | 7 mos. | Hodgkin's disease | Lymphadenoma of chronic hyperplastic variety | Improvement with Roentgen ray, later bacterins added greater improvement | Seven closely similar diphtheroids. M. albus | 0 Rods not destroyed but not acid-fast | Faint, dirty-white, slimy, translucent band | Faint, smooth, brownish-yellow | Limited orange-yellow smear | Faint, flat, orange band becoming brown-gray |

| Bouillon | Potato | Litmus Milk | Gelatin | Inulin | Acidity Reduction | | | | | | | | | Hemolysis | Indol | Pigment | Medium Discoloration | Pathogenic for Guinea-Pigs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Glucose | Lactose | Saccharose | Maltose | Mannite | Glycerin | Dextrin | Galactose | | | | | | |
| Clear sand-like granules | No visible growth | Faintly acid | No visible growth | Alkaline | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Clear sand-like granules and flocculent sediment | Spreading glistening smear, later slightly raised | Faintly alkaline | Faintly turbid liq. 0 | Alkaline | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | See blood serum | Bordet, greenish-brown | |
| Turbid granules; sand-like, flocculent sediment | Dirty white smear, becoming raised and yellowish | Faintly alkaline | Faintly turbid liq. 0 | Alkaline | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | Bordet, greenish; blood agar, brown | |
| Mucoid sediment | No visible growth | No change | No visible growth | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Faint turbidity, flocculent sediment | Luxuriant, spreading, orange | Faintly acid | Luxuriant growth liquefaction + | 0 | + | 0 | 0 | + | 0 | + | 0 | 0 | 0 | + | + | Agar, yellow; Bordet, greenish; potato, orange | 0 | 0 |
| Clear, little flocculent sediment | No visible growth | Faintly alkaline after 12 days | Faintly turbid at top; liquefaction 0 | 0 | − | 0 | − | 0 | − | 0 | − | − | − | 0 | − | + | 0 | + | Blood serum, yellow | Bordet, chocolate-brown | 0 |
| Flocculent sediment | No visible growth | Faintly alkaline | Liquefaction 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | Faint yellow | 0 | 0 |
| No growth | No visible growth | No change | Liquefaction 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | + | 0 | 0 | Faint yellow | 0 | 0 |
| Faint general turbidity; slimy sediment | Glistening, flat, spreading, yellow, becoming brown | Acid coagulation digestion | Liquefaction + | 0 | + | + | 0 | 0 | + | 0 | 0 | 0 | + | 0 | + | + | + | + | Yellowish | 0 | Septicemia in 2 of 3 guinea-pigs |
| Faint turbidity; fluorescent sediment | Yellowish stain | No change | Liquefaction 0; faint turbidity | 0 | + | + | + | 0 | + | 0 | 0 | 0 | − | 0 | + | + | + | 0 | + | 0 | Slight | + | Yellow-brown | Bordet, chocolate-brown | 0 |
| No growth | No visible growth | Coagulation; acidity reduction | Liquefaction 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Yellow-brown | 0 | 0 |

| Case No. | Age and Sex | Duration | Clinical Diagnosis | Pathologic Diagnosis | Vaccine Therapy and Result | Forms of Bacteria Found | Acid and Antiformin Fast | Agar | Blood Agar | Blood Serum | Bordet |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 9265 E. P. | 22 ♂ | 4 wks. | General adenopathy, probably Hodgkin's disease | Lymphadenoma of chronic hyperplastic variety; no eosinophils or necroses | No..... | Cocci do not grow into bacillary forms | ..... | Scanty, slimy, dirty-white | As agar | No perceptible growth | As agar |
| 8772 L. W. | 32 ♀ | 4 mos. | Hodgkin's disease | Endothelioma rapidly growing in lymph channels | Improvement with Roentgen ray, later death | M. albus diphtheroid | 0 Rods not destroyed but not acid-fast | Tiny, delicate, colorless, discrete, round colonies | As agar, but growth and medium becoming brown | Flat, dull, yellowish streak | Dull, brown-green streak of tiny, discrete colonies, medium beneath, chocolate brown |
| 9144-1 I.M.W | 22 ♀ | 6 mos. | Multiple infectious arthritis with adenopathy | ..... | Improvement | Diphtheroids | 0 Rods not destroyed but not acid-fast | Faint, dirty-white, slimy band | As agar | As agar but whiter | Luxuriant, opaque, otherwise like agar |
| 9144-2 | 22 ♀ | 6 mos. | Multiple infectious arthritis with adenopathy | ..... | Improvement | Diphtheroids | 0 Rods not destroyed but not acid-fast | Moist, slimy, opaque, raised, orange to salmon to brown | As agar | As agar; but salmon-yellow becoming pink coral | Just as agar |
| 9202-1 J. M. | 41 ♀ | 7 yrs. | General arthritis, anemia with adenopathy | ..... | Improvement | Diphtheroid | 0 0 | Delicate, raised, moist, opaque, glistening, becoming salmon-pink | As agar, except color pinkish-brown | As agar, except color pale pink | As agar, but color rose pink |
| 9202-2 | 41 ♀ | 7 yrs. | General arthritis, anemia with adenopathy | ..... | Improvement | Diphtheroid coccus | 0 0 | Raised, moist, white, tiny, discrete colonies | At first as agar, then hazy gray, then colonies becoming brown | As agar | Dry, brown, discrete colonies tending to coalesce; medium chocolate brown |
| 9202-3 | 41 ♀ | 7 yrs. | General arthritis, anemia with adenopathy | ..... | Improvement | Diphtheroid coccus | 0 0 | Yellowish-white, small, discrete colonies | Coalescing, grayish growth becoming brown and scanty | Pearl-white, discrete colonies | Dark, dry, greenish-yellow band, causing brown-green discoloration of medium |
| RA-1 767 | 54 ♂ | 4 yrs. | Hodgkin's disease | Hodgkin's disease | Marked improvement | Diphtheroids | 0 Rods not destroyed but not acid-fast | Discrete to confluent, moist, dirty, orange-yellow becoming canary-yellow | As agar, color changes from yellow to dirty brown, with methemoglobin color of medium | Flat, dry, dirty, orange-yellow | Smooth, flat, slightly waxy, spreading, green-brown band; medium brown |
| RA 2 767 | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 Rods not destroyed but not acid-fast | Raised, moist, glistening, slimy, canary-yellow band | As agar, but orange-yellow to greenish becoming brown | As agar | Dry, flat, smooth, opaque, spreading, yellow-brown, medium chocolate |
| RB-1 907 | 48 ♀ | 1½ yrs. | Mediastinal tumor | ? | No improvement | Diphtheroids | 0 Rods not destroyed but not acid-fast | Raised, moist, slimy, glistening, opaque band becoming brown-yellow | As agar, medium dark and opaque | As agar but growth going salmon to orange-yellow to coral-pink | As agar, growth salmon and then red-brown |
| RB-2 907 | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 Rods not destroyed but not acid-fast | Smooth, moist, glistening gray-white band | As agar; hemolysis at top, becoming pale and slimy | As agar, but band becoming pale yellow; medium dark under growth | As agar, but growth dirty brownish gray |
| RB-4 907 | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 Rods not destroyed but not acid-fast | Moist, glistening, dirty-white band | As agar; hemolysis + | As agar but porcelain white | As agar but yellowish becoming dirty yellow-brown |

| Bouillon | Potato | Litmus Milk | Gelatin | Inulin | Acidity Reduction | | | | | | | | Hemolysis | Indol | Pigment | Medium Discoloration | Pathogenic for Guinea-Pigs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Glucose | Lactose | Saccharose | Maltose | Mannite | Glycerin | Dextrin | Galactose | | | | | |
| Faint turbidity | No perceptible growth | Slightly alkaline; no other change | Liquefaction 0 | 0 | + 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | + | 0 | 0 | |
| No visible growth | No visible growth | Very faintly acid | Faint growth liquefaction 0 | Faintly acid | + 0 | 0 0 | + 0 | + 0 | 0 0 | 0 0 | + 0 | 0 0 | 0 | 0 | Dull greenish-brown | Chocolate-brown; green directly under colonies | 0 Rabbits' glands 0 |
| No growth | No visible growth | Faint acidity | Liquefaction 0 | 0 | + 0 | 0 0 | + 0 | + 0 | — 0 | + 0 | + 0 | + 0 | 0 | 0 | 0 | Bordet, gray-brown | 0 |
| Turbid with slimy, yellow sediment | Salmon yellow | Alkaline reduced | Mucoid sediment liquefaction 0 | 0 | 0 + | — 0 | 0 0 | — 3 | — 0 | — 0 | — + | — + | 0 | + | Yellow; salmon pink | 0 | 0 |
| Delicate pellicle and flocculent sediment | As agar | Alkaline; no other change | Liquefaction 0 | 0 | 0 + | — 0 | — 0 | — 0 | — 0 0 | 0 0 | — 0 | 0 + | 0 | 0 | Pink | 0 | 0 |
| No growth | No visible growth | Acid, coagulated, reduced | Liquefaction 0 | 0 | + 0 | + 0 | + 0 | — 3 | 0 0 | 0 0 | + 0 | + 0 | 0 | 0 | 0 | Bordet, chocolate-brown | 0 |
| Faint turbidity; flocculent sediment | No visible growth | Acid, coagulated, reduced | Flocculent sediment liquefaction 0 | 0 | + 0 | + 0 | + C | + 0 | 0 0 | 0 0 | + 0 | + 0 | 0 | 0 | Agar, yellow; Bordet, yellow-brown | Bordet, brown-green | 0 |
| Turbid flocculent sediment | No visible growth | Alkaline; no other change | Heavy flocculent sediment; liquefaction 0 | — | + 0 | — 0 | + 0 | + + | — 0 | — 0 | — + | — + | Methemoglobin | + | Agar, orange-yellow; Bordet, green-brown | Bordet, brown | 0 |
| Faint cloudiness | No visible growth | Alkaline | Turbid, heavy, mucoid sediment | — | + 0 | — 0 | + 0 | + 0 | — 0 | — 0 | — + | — — | 0 | 0 | Agar, yellow; Bordet, yellow-green-brown | Bordet, faint chocolate-brown | 0 |
| Turbid, mucoid sediment | No visible growth | No change | Faint cloudiness, liquefaction 0 | — | 0 + | 0 0 | 0 0 | 0 0 | — 0 | — 0 | — 0 | — + | 0 | 0 | Yellow, orange, pink, brown | Blood agar, dark brown | 0 |
| Turbid, flocculent and granular sediment | No visible growth | Alkaline reduced | Liquefaction 0 | 0 | + + | — 0 | + 0 | + 0 | — 0 | — 0 | — 0 | — + | + | + | Blood serum, yellow | Blood serum, brown | 0 |
| Turbid, flocculent sediment | No visible growth | Alkaline reduced | No change; liquefaction 0 | 0 | + 0 | — 0 | + 0 | + 0 | — 0 | — 0 | 0 0 | — + | + | + | 0 | 0 | 0 |

| Case No. | Age and Sex | Duration | Clinical Diagnosis | Pathologic Diagnosis | Vaccine Therapy and Result | Forms of Bacteria Found | Acid and Antiformin Fast | Agar | Blood Agar | Blood Serum | Bordet |
|---|---|---|---|---|---|---|---|---|---|---|---|
| RC-1 934 | ? ♀ | ? | Hodgkin's disease | Hodgkin's disease | Marked improvement | Diphtheroids | 0 0 | Smooth, flat, moist, glistening spreading, pale blue-gray | As agar, but at first pink, then brown, thengreen; hemolysis + | As agar, later liquefying | Flat, limited, discrete colonies tending to coalesce; gray-brown to red-brown |
| RC-2 923 | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 0 | Slimy, moist, raised, opaque, faint orange band | As agar, but brownish | As agar, but salmon color becoming coral pink | Moist, glistening, deep orange-yellow, becoming ochre |
| RC-3 923 | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 Rods not dissolved | Moist, raised, smooth, glistening limited, white | Yellowish-white, smooth, flat, glistening, discrete to coalescing | Early as minute, yellow, depressed, discrete colonies; liquefaction + | Raised, moist, glistening, discrete to confluent, raised luxuriant, dirty gray-brown |
| RD-1 926 | 29 ♂ | 1½ yrs. | Hodgkin's disease | Hodgkin's disease | Marked improvements | Diphtheroids | 0 Rods not dissolved | Raised, moist, glistening, slimy, dirty white | As agar; pale; hemolysis + | Dry, delicate, dirty white | As agar, rather gray, then pink, with greenish fluorescence in medium |
| RD-2 926 | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 0 | Irregular, discrete to confluent, granular, dirty yellow-white | As agar; hemolysis slight | Smooth, flat, moist, becoming yellowish | Flat, granular, discrete to confluent, waxy, opaque, gray, lusterless |
| RE-1 C | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 0 | Faint, moist, glistening, opaque band | As agar | As agar, but yellow white | Uniform, flat, confluent, gray, with reflection of reddish-brown |
| KI-1 | 24 ♂ | 6-8 wks. | Hodgkin's disease | Hodgkin's disease | No continued improvement, patient died | Diphtheroids | 0 0 | Moist, raised, glistening, opaque, slimy, salmon-yellow band | As agar; medium brown | As agar | As agar; medium opaque brown |
| KII-1 | 40 ♂ | Auto'y 3 mos. duration | Hodgkin's disease | Hodgkin's disease | ..... | Diphtheroids | 0 Rods not dissolved | Faint, almost invisible band seemingly made up of discrete colonies | As agar; medium opaque | As agar | As agar; growth faint grayish-yellow somewhat more luxuriant |
| KII-3 | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 0 | Delicate, dull, moist, dirty white, translucent | As agar | As agar | As agar, becoming more luxuriant, flat, dry, grayish-green |
| KII-4 | .... | ..... | ..... | ..... | ..... | Diphtheroids | 0 Rods not dissolved | Faint streak of discrete, yellow colonies | As agar | As agar | As agar, becoming confluent, dirty gray-brown; medium chocolate brown |
| K* | .... | ..... | ..... | ..... | ..... | ..... | 0 | Glistening, pale gray discrete colonies, becoming confluent and whiter | Similar but luxuriant and raised, medium hemolyzed and then darkened | Glistening, confluent, moist, raised band becoming slightly yellowish | Dull, waxy, brownish band; medium becoming brown and without contrast with growth |
| 872-1† | .... | ..... | ..... | ..... | ..... | ..... | 0 | Luxuriant, glistening, smooth, raised, opaque, dirty white | As agar, more luxuriant and greenish sheen; hemolysis slight | As agar, more luxuriant, raised | Pale salmon-pink, raised, glistening, medium becoming dark brown |
| 872-2‡ | .... | ..... | ..... | ..... | ..... | ..... | 0 | Glistening, smooth, flat, opaque, greenish-white | Glistening, raised, slimy, greenish, hemolysis slight | As agar, more luxuriant becoming lemon-yellow | Somewhat flat, slightly waxy, brownish-yellow, medium darker |

| Bouillon | Potato | Litmus Milk | Gelatin | Inulin | Acidity Reduction | | | | | | | | Hemolysis | Indol | Pigment | Medium Discoloration | Pathogenic for Guinea-Pigs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Glucose | Lactose | Saccharose | Maltose | Mannite | Glycerin | Dextrin | Galactose | | | | | |
| No visible growth | No visible growth | Alkaline reduced | Faintly turbid; liquefaction 0 | 0 | + 0 | — + | + 0 | + + | + 0 | + 0 | + 0 | — + | + | 0 | Greenish, brownish, reddish tinge | 0 | 0 |
| Faint turbidity | No visible growth | Alkaline | Turbid; liquefaction 0 | 0 | 0 + | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 + | 0 | 0 | Orange-yellow to pink | 0 | 0 |
| Turbid; mucoid sediment | No visible growth | Coagulation, faintly alkaline (?), reduction digestion | Liquefaction 0 | Acid reduced | + 0 | — 0 | + 0 | 0 0 | + 0 | + + | + 0 | 0 0 | 0 | 0 | Yellowish-brown | 0 | 0 |
| Turbid, mucoid sediment | Slimy, dirty white | Alkaline | Turbid; liquefaction 0 | 0 | 0 + | — 0 | 0 0 | — 0 | — 0 | 0 0 | 0 0 | — + | + | + | Bordet, fluorescent | See Bordet | 0 |
| Flocculi and granules at bottom | No visible growth | No change | 0 | 0 | 0 0 | 0 0 | + 0 | 0 0 | 0 0 | 0 0 | + 0 | 0 0 | + | 0 | Faint yellow | 0 | |
| Mucoid sediment | No visible growth | Faint acidity | Mucoid sediment; liquefaction 0 | Alkaline | + + | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 + | 0 | 0 | Faint yellow | 0 | |
| Turbid, mucoid sediment | Faint salmon-yellow smear | Alkaline | Mucoid sediment; liquefaction 0 | 0 | — 0 | — 0 | — 0 | — 0 | — 0 | — + | — 0 | — + | 0 | 0 | Salmon | Browning of blood and Bordet | |
| Faintly turbid; slight granular sediment | No visible growth | Faintly alkaline | Faintly turbid; liquefaction 0 | 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 | 0 | 0 | 0 | |
| Faintly turbid; mucoid sediment | No visible growth | Faintly alkaline | Faintly turbid; floating flocculi, liquefaction 0 | Alkaline | + 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | + 0 | + + | 0 | 0 | 0 | 0 | |
| Turbid, flocculent sediment | No visible growth | Faintly alkaline | Turbid at top; liquefaction 0 | Alkaline | + 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | + 0 | + 0 | 0 | 0 | 0 | Bordet, chocolate-brown | 0 |
| Turbid, heavy, flocculent sediment | Delicate smear | No change | Faintly turbid, liquefaction 0 | Acid then neutral | + 0 | 0 0 | 0 0 | + 0 | 0 0 | 0 0 | + 0 | ? 0 | + | 0 | 0 | Bordet, brown | Virulent for guinea-pigs |
| Turbid, heavy, flocculent sediment | Spreading smear, becoming raised and yellowish | Faintly alkaline | Faintly turbid; liquefaction 0 | Alkaline | + 0 | 0 0 | + 0 | 0 0 | — 0 | 0 0 | 0 0 | + 0 | + | 0 | 0 See Bordet | Darkens blood mediums | 0 |
| Clear, thick, tenacious, membrane-like sediment | Faint smear, becoming deep yellow | Faintly alkaline | Faint growth; liquefaction 0 | No change | + 0 | — 0 | + 0 | 0 0 | 0 0 | 0 0 | 0 0 | 0 0 | + | 0 | Yellowish on several mediums | Blood mediums darker | 0 |

* From this patient the true Kleba-Loeffler bacillus has reached the twenty-sixth generation on Loeffler's blood serum.
† In this case the bacillus was of pseudodiphtheria (Winslow, No. 9).
‡ In this case the bacillus was of pseudodiphtheria (spinal fluid, case of cerebrospinal meningitis. Service not explained).

Pirquet is negative. A roentgenogram shows no bone changes in knee and right hand. The Wassermann is negative, the Neisserian fixation-test is negative. The epitrochlear gland is sterile.

Section shows lymphadenoid tissue in a state of chronic follicular and interstitial formation. In the chords and sinuses one may see endothelial and large lymphocyte hyperplasia, and there is a prominence of the vascular endothelium. The connective tissue, both in the gland and in the capsule, is increased, hyaline and poor in cells. Diagnosis, chronic lymphadenitis.

The first two cases (6638, 6640) correspond to the picture accepted as that of Hodgkin's disease, and from them were isolated diphtheroid organisms of quite similar morphology but distinctly differing in biology (Figs. 1 to 6). They are similar in Loeffler's stain to R. B. 2 (Figs. 39 and 40), R. E. 1 (Figs. 50 and 51), and K. II-3 (Fig. 54). Vaccine treatment is now being given in both these cases but no report can be given yet as to its action.

The third case is one of Hodgkin's disease from its history and was so diagnosed by Dr. Stengel. The histologic section does not show the picture required but it should be remembered that Roentgen-ray treatment had been used for several months before the gland culture was made. This would probably alter the anatomy of the tissue. From this case no less than seven slightly varying bacteria were found (Figs. 7 to 23). Among these Nos. 1 (Figs. 7 to 10), 4 (Figs. 15 to 17), and 7 (Figs. 18 to 20) most resemble the cultures in the frank cases of Hodgkin's disease as given above. There are certain similarities between these and some of the cultures of Drs. Rosenow and Kolmer.

The fourth case was probably one of Hodgkin's disease although certainly far from typical; only cocci were culturable.

In the fifth case, Patient McC., unfortunately, the culture failed to give a growth and he died so soon after the operation that further work was impossible. It would have been interesting to have gotten a growth in his case because in the next case, another endothelioma, there was a prompt growth of a long rod (8772, Figs. 25 to 29). This organism bears no resemblance to any other of my own cultures but is quite like R. C. 3 (Figs. 45 to 47); Dr. Rosenow marks this case as one of Hodgkin's disease. This bacterium is not at all like those in my cases of frank Hodgkin's.

From the sixth and seventh cases, diagnosed as tuberculosis by the finding of the bacilli, no rods could be cultivated. The histologic sections from the case of A. G. F. were studied by Gram-Weigert, Giemsa and Much stains. Here and there a solidly staining gram-positive rod (probably a tubercle bacillus) was found, but no granules like the Much granules or rows of beads such as he has described in Hodgkin's disease were seen.

The last five cases are instances of arthritis, from two of which interesting cultures were obtained. 9144-1 (Fig. 30) resembles rather closely R. B. 2 (Fig. 40) and R. E. 1 (Figs. 50 and 51), and is like a small example of 8916-9 (Figs. 21 and 22), while 9392-1 (Figs. 32 and 35), although drawn with difficulty because of its poor staining properties, is similar to 6640 (Fig. 5). Neither of these cases even remotely resemble Hodgkin's disease and it is noteworthy that diphtheroids were found in them.

## GENERAL DISCUSSION

Examination of the charted characters, the morphology notes and the pictures reveals a bewildering variety of organisms, closely related diphtheroids and a few cocci. To dispense with the latter it may be pointed out that they were *M. albus* in two cases (8772 and 8916), two slightly varying streptococci in an arthritis case (9392) and a large diplococcus in a possible Hodgkin's case (9265). In this instance the remark of Dr. Rosenow may be recalled, to the effect that cocci predominate in the more recently enlarged glands. This glandular enlargement was only of four weeks' duration.

Consideration of the diphtheroids fails to show any two alike, and as has been suggested in discussing the case groups there is no marked similarity between cultures isolated from closely related pathologic conditions, with the possible exception of the two frank Hodgkin's cases, 6638 and 6640. In the first of these two there were three pseudodiphtheria bacilli, one of which resembles morphologically the single bacterium isolated from 6640, being distinct in its cultural characteristics.

It does not seem profitable to attempt any conclusions from this series of 13 cases, even in conjunction with the material given me by Dr. Rosenow and Dr. Kolmer, further than to state that no one bacterial variety with definite morphologic and cultural characters has been isolated from eleven cases diagnosed as Hodgkin's disease (Rosenow 5, Kolmer 2, my own cases 4) to which may be added a case of endothelioma of the lymph nodes. Diphtheroid bacilli have been isolated from glands in at least two cases having no clinical or anatomic resemblance to Hodgkin's disease and from Case C. of Dr. Rosenow, an instance of mediastinal tumor. Much work will be necessary to establish the microbic cause of Hodgkin's disease especially in the direction of immunology. This I have already begun but I have not as yet sufficient data to make it worth discussing. Two of the cases have failed to show agglutination of the bacteria isolated in them, and one did not bind complement with the patient's serum.

A study of the duration of enlargement of the gland supplying the cultures and the bacteriologic result reveals nothing. The position of the gland seems to have nothing to do with the kind of organism

isolated. In the Hodgkin's and similar cases material was removed from the inguinal region twice, axilla and mastoid region each once. The endothelioma was in the cervical glands. The arthritis cases giving positive cultures supplied respectively an axillary and epitrochlear gland. The position of these last two glands is such that drainage from the throat and genital tract, the common habitats of diphtheroids, is probably excluded as a means of their recent reception. However, they probably entered through one of these places at some time.

The glands of the patients in the two frank Hodgkin's cases and the tuberculous adenitis case, A. G. F., have been studied by the Much, Gram-Weigert and Ziehl-Nielson stains. Tubercle bacilli have been found only in the last case. No Much granules, either single or in rows were found in the first two. By the Much method a few diphtheroids were found in 6640 as pale rods with poorly staining, large, blue granules. No metachromatic bodies were found. Only one rod was found in the Gram-Weigert preparations and it was nearly solidly blue.

The material presented here may be summed up as follows:

Diphtheroid rods may be isolated from Hodgkin's disease and other adenopathies, but there is no uniformity in biology and morphology among the strains isolated by three observers from clinical and pathologic Hodgkin's disease. Diphtheroid rods, similar in biology and morphology to those found in Hodgkin's disease, may be found in enlarged glands in cases of chronic atrophic arthritis and other conditions.

Diphtheroids have been found in glands the seat of a neoplasm (8772), and in the enlarged glands near a neoplasm (R. C.). There is great similarity in all respects between the gland diphtheroids and those found in normal and pathologic seats in the body, the so-called pseudodiphtheria bacilli. More facts are demanded to show the exact relation of the diphtheroids to Hodgkin's disease.

In one case, in which autogenous vaccination was given a fair trial, the patient has died.

Another patient, already improving under the Roentgen ray, continued to improve with autogenous vaccination and no Roentgen ray. In arthritis cases the patients receiving vaccine consisting wholly or in part of diphtheroids, showed some improvement.

Much granules have not been found in sections of lymph granulomas of the Hodgkin's type.

The cases used in this work were in the services of Dr. Stengel, Dr. Frazier, and Dr. A. C. Wood at the University Hospital. I wish to thank these gentlemen for the use of the material.

I am indebted to Mrs. V. C. Brogdon for much assistance in running through cultures and for the preparation of the chart, and to Miss L. H. Irwin for the drawings.

# THE DIMINISHED POWER OF THE NEPHRITIC KIDNEY FOR ELIMINATING URIC ACID AS EXEMPLIFIED BY THE USE OF ATOPHAN *

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It is presumed that in normal and gouty individuals atophan induces an augmented output of uric acid in the urine and a decreased concentration in the blood (and tissues) by endowing the renal cells with an increased power for eliminating uric acid.[1] In nephritis,[2] accordingly, the renal cells, which have become abnormal and whose work has been impeded by interstitial growth, would be expected to respond less readily to this stimulus. In the present communication are presented six cases of nephritis, which illustrate the diminished, or entire absence of any, effect of atophan on the concentration of uric acid in the blood.[3]

The observations in Case 1 were made before the onset of marked uremic symptoms. The reduction in the uric acid concentration of the blood following the use of atophan is relatively slight, in accordance with which there is no demonstrable increase in the urinary uric acid. Other blood findings and the very low phenolsulphonephthalein output give further evidence of inefficient renal functioning.

Case 2, taken at a more advanced stage than Case 1, while uremic symptoms were pronounced, disclosed no reaction to atophan whatever. This is significant in view of the failure of any injected phenolsulphonephthalein to reappear in the urine, and the notable retention of urea and creatinin as well as uric acid in the blood.

Case 3, clinically, was in far better condition during the period of observation than the two cases above discussed, although a week later the patient suddenly developed convulsions and died. One notes that on two occasions there were moderate responses to the administration of atophan. The urinary findings are not always in good agreement with the blood changes, but this is attributed to faulty collection and

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1. Fine and Chace: Jour. Pharm. and Exper. Therap., 1914, vi, 219.

2. Cf. Folin and Lyman: Jour. Pharm. and Exper. Therap., 1913, iv, 539.

3. We are indebted to Drs. R. A. Cooke and W. G. Lough for many courtesies extended to us in the course of this study, and to Mr. Adolph Bernhard for the determinations of uric acid in the urine.

TABLE 1.—Slight Effect of Atophan in Nephritis (Case 1, T. D.) Before Onset of Marked Uremic Symptoms *

| Day | Uric Acid in Urine gm. | Uric Acid in Blood mg. per 100 c.c. | Atophan gm. per day |
|---|---|---|---|
| 1 | 0.13 | | |
| 2 | 0.16 | | |
| 3 | 0.13 | | |
| 4 | 0.21 | 6.8 | |
| 5 | 0.08 | ... | 1 |
| 6 | 0.11 | ... | 1 |
| 7 | 0.14 | ... | 1 |
| 8 | 0.09 | ... | 3 |
| 9 | 0.13 | ... | 3 |
| 10 | 0.13 | ... | 3 |
| 11 | 0.11 | 6.0 | |
| 12 | 0.07 | | |
| 13 | 0.10 | | |
| 14 | 0.07 | | |
| 15 | 0.16 | | |

* Male, aged 34 years. Diagnosis, advanced interstitial nephritis with marked cardiac hypertrophy. Blood pressure, 230 (systolic), 130 (diastolic); phenolsulphonephthalein output, 3 to 4 per cent. (two determinations); urine: 0.2-0.3 per cent. albumin, moderate number hyaline and granular casts. Other blood findings: urea N, 100; creatinin, 8 mg. per 100 c.c. Died six weeks after conclusion of the observations. Diagnosis confirmed at necropsy and by histological examination.

TABLE 2.—Advanced Case of Nephritis (Case 2, K. K.) with No Reaction to Atophan *

| Day | Uric Acid in Blood mg. per 100 c.c. | Atophan gm. per day |
|---|---|---|
| 1 | 12.3 | 1 † |
| 2 | .... | 2 |
| 3 | 12.5 | 2 |

* Female, aged 39 years. Diagnosis, chronic interstitial nephritis (uremia). Blood pressure eight days before death, 265 (systolic), 140 (diastolic); phenolsulphonephthalein output, 0 (two determinations); urine: large amount of albumin. Other blood findings: urea N, 148; creatinin, 15 mg. per 100 c.c. No edema. Died day after conclusion of above observations.

† After taking blood.

TABLE 3.—Moderate Response to Atophan in Case of Nephritis (Case 3, J. W.) Clinically in Good Condition *

| Day | Uric Acid in Urine Daily Averages gm. | Uric Acid in Blood mg. per 100 c.c. | Atophan gm. per day |
|---|---|---|---|
| 1 | .... | 8.1 | |
| 2–5 | 0.15 | | |
| 7 | .... | ... | 2 |
| 8 | .... | ... | 2 |
| 9 | .....0.24 | ... | 4 |
| 10 | .... | ... | 4 |
| 11 | .... | 6.0 | 4 |
| 12–16 | 0.15 | | |
| 17–29 | 0.17 | | |
| 30 | .... | 7.0 | 1† |
| 31 | .... | ... | 1.5 |
| 32 | .... | ... | 3 |
| 33 | .....0.15 | ... | 3 |
| 34 | .... | ... | 3 |
| 35 | .... | ... | 4 |
| 36 | .... | 5.4 | |
| 36–40 | 0.24 | | |
| 44 | .... | 7.2 | |

* Male, aged 34 years. Diagnosis, chronic interstitial nephritis. Blood pressure, 170 (systolic), 100 (diastolic); phenolsulphonephthalein output, 4 per cent. in two hours; urine, approximately 0.1 per cent. albumin, occasional hyaline and granular casts, few pus cells. Other blood findings: urea N, 50; creatinin, 6 mg. per 100 c.c.

† After taking blood.

TABLE 4.—No Response to Atophan in Nephritis (Case 4, S. H) *

| Day | Uric Acid in Blood mg. per 100 c.c. | Atophan gm. per day |
|---|---|---|
| 1 | 7.7 | |
| 2 | ... | 3 |
| 3 | ... | 3 |
| 4 | ... | 4 |
| 5 | 8.0 | |

* Male, aged 37 years, interstitial nephritis (uremia). Phenolsulphonephthalein output, 1 per cent. in two hours; urine: moderate amount albumin, occasional hyaline and granular cast. Other blood findings: urea N, 70; creatinin, 10 mg. per 100 c.c. Slight edema of extremities. Patient died six weeks after observations were concluded.

TABLE 5.—Definite Response to Atophan in Nephritis (Case 5, J. P.) Clinically in Good Condition *

| Day | Uric Acid in Blood mg. per 100 c.c. | Atophan gm. per day |
|---|---|---|
| 1 | 6.7 | |
| 2 | ... | |
| 3 | ... | 2 |
| 4 | 6.0 | 3 |
| 5 | ... | 3 |
| 6 | ... | 2 |
| 7 | 4.3 | |
| 8 | ... | |
| 9 | 5.7 | |
| 12 | 6.8 | |

* Male, aged 34 years, chronic diffuse nephritis. Phenolsulphonephthalein output for two hours, 43 per cent. Urine: moderate amount albumin, many hyaline and granular casts. Other blood findings: urea nitrogen, 25; creatinin, 2.5 mg. per 100 c.c. Wassermann ++++.

TABLE 6.—Decided Response to Atophan (Case 6, L. S. M.) *

| Day | Uric Acid in Blood mg. per 100 c.c. | Atophan gm. per day |
|---|---|---|
| 1 | 5.0 | 2‡ |
| 2† | ... | 3 |
| 3 | ... | 3 |
| 4 | 2.7 | |
| 7 | 4.0 | |

* Female, aged 23 years. Subacute parenchymatous nephritis. Blood pressure, 110 (systolic), 65 (diastolic); phenolsulphonephthalein output, 31 per cent. in two hours; urine: moderate amount albumin, occasional hyaline and granular cast, few pus cells. Other blood findings: urea nitrogen 22, creatinin 25 mg. per 100 c.c. Pregnant four months previous to present study, at which time edema was present. No edema during above period of observation.

† On this day the milk contained 2.7 mg. uric acid per 100 c.c. ‡ After taking blood.

inadequate preservation of the urine. The urea and creatinin concentrations of the blood indicate a less pronounced retention than that observed in the two previous cases.

Case 4 showed no response whatever to the administration of atophan, which is in harmony with the pronounced retention of creatinin and the negligible output of phenolsulphonephthalein. The clinical prognosis is an early fatal termination.

Case 5 shows a definite response to atophan, to the extent of a reduction of blood uric acid of 2.4 mg. per hundred c.c. This favorable sign falls in with the moderate retention of urea nitrogen and creatinin and the quite good output of phenolsulphonephthalein. Clinically, the case at present appears not to be in a serious condition.

In Case 6 the response to atophan is quite decided, which is of interest in connection with the fair elimination of phenolsulphonephthalein and the but slightly increased urea and creatinin concentrations of the blood.

It is evident that in these six cases there is a general relationship between the degree of response to the administration of atophan on the one hand, and the extent of non-protein nitrogenous retention and the clinical pictures on the other. While we hesitate, on the basis of these all too few cases, to formulate definite conclusions, the observations do appear to us to lend some support to the view enunciated in the opening paragraph of this paper that abnormal renal cells would be expected to prove less responsive to the action of atophan than are healthy cells.

After a part of our data had been accumulated, the paper of Frank and Pietrulla[4] came to our attention. They reported four abnormal kidney cases, in which atophan was employed. In their first case (contracted kidney) the uric acid concentration of the blood was reduced from 3.0 mg. per hundred c.c. to 0. In their second case (bilateral cystic kidney) it was reduced from 1.5 to 0. The low concentrations of blood uric acid in these two instances indicate that they were not the type of case in which the kidneys would be expected to offer opposition to the action of atophan. In their third case (contracted and cystic kidney) the uric acid concentration of the blood was not determined before atophan was given, but since after the administration of the drug the moderately high value of 4.78 mg. per hundred c.c. was noted, they considered the previous existence of a higher concentration as improbable. This is an unjustified stand, as indicated in our present studies and by several others elsewhere reported,[5] in which

4. Frank and Pietrulla: Arch. f. Exper. path. u. Pharmakol., 1914, lxxvii, 361.
5. Myers and Fine: Jour. Biol. Chem., 1915, xx, 391.

values of 8 to 15 mg. per hundred c.c. of blood were commonly observed. In their fourth case (subacute nephrosis) they describe the atophan effect by reporting many typical crystals before and fewer after the use of the drug. The results of Frank and Pietrulla, above reviewed, appear too indecisive to throw light on the question of the dependence of an atophan response on the condition of the renal cells.

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# CHRONIC MENINGOCOCCUS SEPTICEMIA ASSOCIATED WITH PULMONARY TUBERCULOSIS*

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The earlier clinical and pathologic studies of certain infectious diseases, among others, pneumonia, typhoid fever, gonorrhea and epidemic meningitis, indicated a marked predilection of the specific excitant to localize in certain definite tissues. The introduction of more accurate methods for clinical investigation, and of additional refinements in bacteriologic technic have afforded substantial evidence that the distribution of the causal agent in such disorders is not so limited as was formerly presumed.

Following the identification in 1887 of the *Meningococcus intracellularis* by Weichselbaum[1] as a separate species, and the establishment of its specific relation to epidemic meningitis, investigations were conducted to determine the presence of this microorganism in the blood and in the lesions complicating this disease.

The biologic characteristics of the meningococcus rendered such investigations particularly difficult. The susceptibility of the organism to outside influences and its intracellular position made it difficult to cultivate under the most favorable conditions. Bacteria other than the meningococcus frequently encountered in such investigations often obscured the cultural characteristics of the meningococcus by the production of a more luxuriant growth, and thus led to negative findings. It has also been quite definitely determined that certain bacterial species, among others, the *Micrococcus catarrhalis* of Pfeiffer, the gonococcus, certain strains of the *Diplococcus flavus, Micrococcus pharyngius siccus, Diplococcus crassus, Micrococcus cinerus* and pseudomeningococcus are similar to the meningococcus in their morphology, tinctorial reactions and occasionally in their intracellular position.

Investigators at present are agreed that the microscopic findings alone are inadequate for purposes of differentiation, and that data regarding the cultural characteristics and biologic activities of the organism are necessary before a bacteriologic diagnosis can be made with any degree of certainty. The many alleged reports of the pres-

* Submitted for publication May 5, 1915.
* Read before the Saranac Lake Medical Society, at Saranac Lake, N. Y., Dec. 9, 1914.

1. Weichselbaum: Fortschr. d. Med., 1887.

ence of the meningococcus in parts removed from the central nervous system, or in the circulating blood, must therefore be accepted with reserve if the identification rests merely on microscopic examination.

Antedating the discovery by Weichselbaum of the specific nature of cerebrospinal fever, Gaucher[2] in 1881, in an epidemic of meningitis, observed numerous cocci in the cerebral exudate, blood and urine. Ughetti[3] in 1883 demonstrated cocci in the spinal exudate and blood in a case of meningitis. The brief bacteriologic notes included in both the above reports do not permit a definite opinion regarding the nature of the organism described. In 1905 Martini and Rohde[4] reported two cases of meningococcus septicemia occurring in epidemic meningitis. They state that to their knowledge this is the first instance in which the organism has with certainty been microscopically and culturally demonstrated in the blood. Cochez and Lemaire,[5] 1901, are credited by Kutscher[6] as the first to report an authentic case of meningococcus septicemia. In an epidemic of cerebrospinal fever they examined the blood eleven times and obtained positive findings in two cases. Duval,[7] Boviard[8] and others, however, concede the claim of priority to Gwyn[9] who reported in 1899 a case of epidemic meningitis complicated by arthritis. A gram-negative diplococcus was recovered from the synovial and spinal exudates, and from the blood. The organism isolated by Gwyn displayed the ability to grow on solid gelatin, a characteristic which Albrecht and Ghon,[10] Weichselbaum,[11] Kutscher,[12] Kolle and Wassermann[13] and others have failed to demonstrate as belonging to the meningococcus. With this one exception, the evidence appears conclusive that the organism isolated in this case was a true meningococcus.

Meningococcus septicemia accompanying or secondary to meningitis has been reported by Lenhartz,[14] Marcovitch,[15] Robinson[16] and

2. Gaucher, quoted by Weichselbaum: Kolle and Wassermann's Handb. d. path. Mikroorg., Edit. 1, iii.
3. Ughetti, ibid.
4. Martini and Rohde: Berl. klin. Wchnschr., 1905, xlii, 997.
5. Cochez and Lemaire: Baumgarten's Jahresbericht, 1902, xviii, 91.
6. Kutscher: In Kolle and Wassermann's Hand. d. Path. Mikroorg., Edit. 2, iv.
7. Duval: Jour. Med. Research, 1908, xix, 258.
8. Bovaird: THE ARCHIVES INT. MED., 1909, iii, 267.
9. Gwyn: Bull. Johns Hopkins Hosp., 1899, x, 112.
10. Albrecht and Ghon: Wien. klin. Wchnschr., 1901, xiv, 984.
11. Weichselbaum: Handb. d. path. Mikroorg., Edit. 1, iii.
12. Kutscher: Munchen. med. Wchnschr., 1906, No. 20.
13. Kolle and Wassermann: Klin. Jahrb., 1906, xv.
14. Lenhartz: Deutsch. Arch. f. klin. Med., 1905, lxxxiv, 81.
15. Marcovitch: Wien. klin. Wchnschr., 1906, xix, 1312.
16. Robinson: Am. Jour. Med. Sc., 1906, cxxxi, 603.

others. Elser[17] in a careful study of forty-one cases of cerebrospinal fever recovered the intracellular diplococcus from the blood in ten, or approximately 25 per cent.

Duval[7] states that a careful review of the literature of meningococcus septicemia would seem to indicate that septicemia due to the meningococcus is invariably secondary to meningitis. It has, however, been definitely established that meningococcus septicemia can occur with no evidence of a previous or existing meningitis.

The following case reported by Andrews[18] in 1906 is of special interest in this respect:

A physician, aged 50, suddenly developed a few spots on the face and within a few hours was covered from head to foot with a profuse hemorrhagic purpura. The temperature was 99.4 F., respirations 34 per minute; pulse not perceptible at the wrist. The appearance of the patient suggested a profound sepsis. He lapsed into unconsciousness and death occurred twenty-four hours from the onset of the illness. There were no meningeal symptoms. The result of the blood examination made shortly before death showed large cocci on the blood films, which were exclusively intracellular, and the blood culture yielded a gram-negative coccus which corresponded in every detail to the diplococcus of Weichselbaum. At necropsy there was no macroscopic or microscopic evidence of meningitis. The case, however, was of very short duration, and of a fulminating type.

Cecil and Soper[19] have more recently described an interesting case of meningococcus endocarditis with septicemia. The complete bacteriologic data included in this report leave no room for doubt as to the identity of the organism. At postmortem the meninges and brain appeared normal. Microscopic sections of the various parts of the cortex, pons and medulla showed a normal pia arachnoid and offered nothing suggestive of an exudate.

A number of further cases have been selected from the literature as they present clinical pictures similar in many respects to the case to be described. In 1902 Salomon[20] reported the following case:

The patient, a woman, aged 32, complained of pain and swelling in the hands, elbows and knees. These symptoms were followed by chills and fever. A few days later, owing to the septic appearance of the patient and the presence of a skin eruption, a blood culture was taken and submitted to Professor Marx of the Royal Institute for Experimental Therapy at Frankfort, who reported the organism to be a meningococcus. The condition of sepsis continued over a period of eight weeks, with no evidence of meningitis or focal involvement except a slight splenic enlargement. Successive fresh crops of a multiform eruption appeared, resembling erythema exudativa, petechia and at time a syphilic or typhoid roseola. The nodules on the feet were tender to pressure. Eight weeks after onset, typical symptoms of meningitis developed. The collected fluid removed by lumbar puncture contained gram-negative diplococci, mostly intra-

17. Elser: Jour. Med. Research, 1905, xiv, 89.
18. Andrews: Lancet, London, 1906, lxxxiv, 1172.
19. Cecil and Soper: The Archives Int. Med., 1911, viii, 1.
20. Salomon: Berl. klin. Wchnschr., 1902, xxxix, 1045.

cellular. The culture from the spinal fluid proved sterile. The patient eventually recovered after an illness of more than four months.

The description of the organism isolated is as follows: It grew only at incubator temperature on nutrient agar and blood agar. By continued cultivation of the organism a growth was eventually obtained on plain agar. Transplants to plain bouillon, gelatin and potato were negative. The coccus was gram-negative, biscuit shaped and was occasionally observed in short chains. Mice remained healthy after a subcutaneous injection of one platinum loopful of a suspension of agar culture in bouillon, but death resulted after an intraperitoneal injection of the same amount.

No serum reactions were recorded. As there is no record of a lumbar puncture having been made previous to the development of the meningeal symptoms, the presence of meningitis early in the disease cannot be excluded with certainty. One is forced, however, to believe that the meningococcus septicemia antedated the meningitis or that the meningeal involvement remained latent over a period of two months before manifesting symptoms.

Liebermeister[21] reported the following case in 1908:

A laborer, aged 59, was admitted to the hospital Feb. 25, 1908, complaining of general malaise with pain and stiffness in both shoulders. The patient claimed to have had inflammation of the lungs on two previous occasions. The statements of the patient were conflicting and the mentality was not entirely clear. Definite signs of pulmonary involvement were present, and the spleen was slightly enlarged. The symptoms and fever were of the septic type. Repeated crops of small papules and rose-like spots appeared. The knee and elbow joints were painful, stiff and contracted. There was no evidence of meningitis. After an illness of four months the patient finally recovered. Several cultures from the blood yielded the meningococcus. The spinal fluid remained normal. Repeated examinations of the sputum failed to show tubercle bacilli, but contained numerous pneumococci. The organism isolated conformed in all essentials to Weichselbaum's coccus. The administration of Wassermann's serum previous to the agglutination tests invalidates to some extent the positive results obtained.

As the patient recovered, meningitis cannot be excluded, but the sterile spinal fluid and absence of meningeal symptoms constitute strong evidence that no meningeal involvement occurred.

Fukuhara[22] summarizes a report by Handa and Nanjo of an epidemic of cerebrospinal fever occurring in a regiment stationed at Osaka.

The nine cases comprising the epidemic were studied clinically and bacteriologically in detail. Five of the cases were to be looked on as suffering from a bacteremia; in four, the meningococcus was cultivated from the blood. One of the cases showed first on the twenty-first day, a second on the twenty-third day, and a third after several months, the typical symptoms of cerebrospinal meningitis. The cerebrospinal fluid, which was at first quite clear, and bacteria-free, became turbid and contained the diplococcus of Weichselbaum.

21. Liebermeister: Munchen. med. Wchnschr., 1908, lv, 1978.
22. Fukuhara: Centralbl. f. Bakteriol. and Parasitol. Ref., 1914, No. 3, p. 82.

The authors conclude from their observations that epidemic meningitis begins as a bacteremia, and that the meningeal symptoms follow as a later manifestation.

## SUMMARY OF AUTHOR'S CASE

Patient A. D., aged 39, Canadian, married, linotypist, had an irrelevant family history. His wife and four children are well. One infant died of convulsions eight years ago. He uses tobacco and alcohol moderately. Venery is denied.

*Past History.*—Except for the early diseases of childhood and occasional attacks of acute indigestion, the patient enjoyed excellent health until May, 1913, when he had general malaise—cough with considerable expectoration and loss of weight, and complained of pain at the base of the right lung. The sputum was blood-streaked on several occasions and contained tubercle bacilli. The patient entered Iola Sanatorium where he remained two months and was then referred to us for further treatment. He presented on examination a slight involvement at the right apex and dense infiltration at the corresponding base; otherwise the examination was negative. Excellent progress was made during a treatment period of seven and one-half months, and the patient was discharged April 16, 1914, with the pulmonary condition arrested. He remained well for three months, when he had a chill with temperature following a prolonged exposure to a cold, drenching rain on a fishing expedition. Patient returned to work on the second day, but as the chills and fever recurred, applied to the sanatorium for readmission, July 5, 1914. The patient appeared obviously toxic and complained of severe pain in the legs. Temperature 103.2 F.; pulse 102; respiration 24. The next day and for two subsequent days, he was quite comfortable, when the symptoms and pain again appeared. Urgent family matters arose at this time, which made it imperative for him to return home for a period of six weeks. Dr. Trembley has kindly supplied me with the following notes of the case during this interval. The patient was free from symptoms and worked for two weeks after leaving the sanatorium, when he again ventured on a second fishing expedition; was exposed to an all day cold rain, which resulted in a return of the chills and fever. From this date, similar attacks recurred, at first, two to five days apart, but toward the end of August, daily. The symptoms suggested malarial fever, but repeated examinations of the blood failed to show the plasmodium. Leukocytes, 13,000; polymorphonuclears, relatively and quantitatively increased. The administration of large doses of quinin and aspirin seemed to influence the symptoms and temperature favorably.

On September 8 the patient again came under our observation. Only the more important findings are here recorded. He was greatly emaciated, having lost at least 30 pounds since last seen; he was somewhat prostrated and appeared acutely ill. The features were blanched but not cyanotic. He responded intelligently to questions. The pupils were equal and reacted to light and accommodation. There were no ocular palsies. Ears, nose and throat were normal. The pulmonary condition failed to present any evidence of recent activity. The size and position of the heart was difficult to define, owing to the pulmonary lesion, but apparently no hypertrophy of the organ existed. At the cardiac apex a faint systolic murmur transmitted toward the axilla for a short distance was heard; other valvular orifices were intact. The pulse was 96, regular, of fair volume; the arterial wall was soft. No enlargement of the spleen was made out on palpation or percussion, and the abdomen contained nothing worthy of note. The superficial and deep reflexes were slightly accentuated. The knees, elbows and some of the smaller joints of the hands were flexed, stiff, slightly swollen and painful, with no reddening of the overlying skin. The anterior surface of both tibias and the muscles of the extremities

were decidedly painful to light pressure; the large nerve trunks were not. There was a diffuse multiform eruption of the skin, more abundant on the arms and legs, irregularly distributed, and composed for the most part of macules or slightly raised papules, which showed a pigmented center and hyperemic zone; the spots varying in size from a pinhead to 3 cm. in diameter. In the older spots the hyperemic zone had been replaced by a discolored area or was entirely lost, giving to the latter a flea-bite appearance. On both thighs anteriorly and on the right leg there were a few large hyperemic nodules, which were exquisitely tender and resembled erythema nodosum. On the abdomen and back, a few rose spots typical of a typhoid roseola were seen. The face and the mucous membranes of the mouth and nose were free from the eruption. The bowels were regular, the appetite poor, temperature 103 F.; respiration 20, pulse 96.

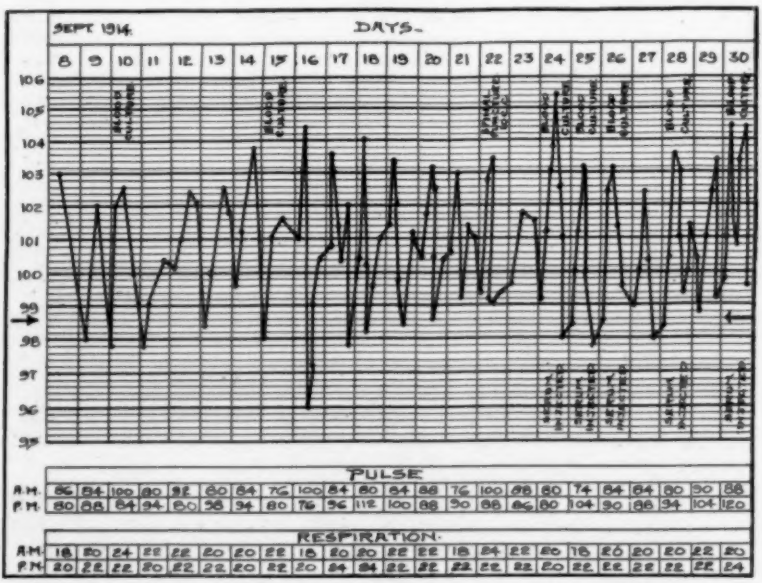


Chart 1.—Patient's pulse, temperature and respiration record during September, 1914.

September 9: Cough and expectoration are slight. The sputum, mucopurulent, 10 c.c. in twenty-four hours, contained tubercle bacilli. There was no thoracic pain or obvious dyspnea. Leukocytes, 13,900; polymorphonuclears, 75 per cent.; red blood cells, 4,100,000; hemoglobin, 80 per cent.

September 10: The quiescent condition of the tuberculous lesion and the absence of local symptoms pointing to an acute respiratory disorder, would incline one to believe that the patient's condition could not be satisfactorily explained on the basis of a recrudescence of the pulmonary lesion. This idea was further enforced by the unusual clinical course which presented features foreign to a tuberculous infection. The septic appearance of the patient, associated with a cardiac murmur, petechial eruption and involvement of several joints suggested a wide generalization of the causal agent, the blood presumably

acting as the channel of distribution. A blood culture[23] was taken. Ten c.c. of blood were withdrawn from the median vein, and immediately transferred to a flask containing 150 c.c. of plain bouillon.

September 12: Swelling and tenderness of the left testicle appeared. An ice cap was applied. Patient was somewhat weaker and complained bitterly of pain in both tibias. Morphin was required to alleviate the pain.

September 15: Swelling and pain in the testicle has completely subsided. The accompanying temperature chart illustrates the intermittent type of fever. Increase of symptoms accompanied the rise in temperature, but the mentality of the patient, though clouded, was not more than would accompany the degree of fever present. The knees and elbows remained slightly flexed and could not be fully extended without producing considerable pain. No exudate into the joints had occurred and the overlying skin was not inflamed. The blood culture of September 10 was positive. Microscopically and culturally the coccus isolated conformed in all essentials to the diplococcus of Weichselbaum. A detailed report of the bacteriologic findings is found elsewhere in this article. Second blood culture, 10 c.c., was made to verify the bacteriologic report. Leukocytes 13,100.

September 16: The patient's condition is not noticeably changed. Fresh crops of eruption appear, more abundant on the thighs. The unexpected nature of the organism disclosed and its invariable association with meningitis made us repeat the examination of the nervous system in detail. The eyes showed no abnormal change. Examination of the cranial and spinal nerves elicited nothing of note. There were no areas of anesthesia, hyperesthesia or paresthesia. The deep and superficial reflexes remained somewhat accentuated. Babinski and Brudinski signs were negative. Owing to the flexed condition of the knees and pain on extension, no opinion could be formed as to the presence or absence of Kernig's sign.

September 18: There was a systolic murmur over the pulmonic area; the mitral murmur was very faint. The ratio between the pulse and temperature was definitely altered, the pulse rate rarely exceeding 110 with a temperature registering 104 F. or above. A few small hyperemic papules on the fingers of the right hand and a solitary large red nodule, 3 cm. in diameter, on the inner side of the same elbow were noted. The skin over the metacarpophalangeal joint of the little finger was reddened and the joint was swollen and tender. No definite chills had as yet been noticed.

September 22: Ten c.c. of spinal fluid were withdrawn. The fluid was not under pressure and was of an opalescent appearance. A scarcely visible precipitate was formed after centrifuging for ten minutes. Stained smears of the sediment showed a few leukocytes, red blood cells, but no bacteria. The sediment was planted on ascitic broth and blood agar. No growth appeared. The cell count and chemical tests were not carried out. A sterile swab was inserted through the mouth into the nasopharynx. The culture obtained yielded gram-positive and gram-negative cocci; the cultural behavior of the latter conformed to the *Micrococcus catarrhalis*. Fresh crops of the eruption with the characteristics already described appeared from time to time. Leukocytes 18,500. The urine showed a slight trace of albumin. Diazo and indican reactions were negative.

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23. Technic: The anterior surface of the elbow joint was scrubbed with green soap and sterile water, followed by a 1:1,000 solution of mercuric chlorid, alcohol and ether; then thoroughly dried with a sterile swab, and tincture of iodin applied. The arm above the elbow was sufficiently compressed by a Bier's bandage to produce an engorgement of the median basilic or cephalic vein, which was selected for taking the culture. A sterile all glass Luer syringe (15 c.c. capacity) and No. 18 or 19 needle were used. Sterile rubber gloves and gown were worn by the operator.

September 23: Certain features of the case, more especially the septic course of the disease, complicated by a polyarthritis, orchitis, cardiac lesion and the presence of gram-negative cocci in the blood suggested a systemic gonococcus infection. The culture taken from the urethra after a thorough massage of the prostate yielded a gram-positive coccus. Complement fixation test for the gonococcal infection was negative. A second culture from the nasopharynx yielded a staphylococcus. Unsuccessful attempts were made to demonstrate intracellular cocci on blood smears. An antiseptic solution for the nose and throat was ordered. The second blood culture of September 15 yielded the meningococcus.

September 24: The well-recognized value of serum treatment in epidemic meningitis suggested its employment in the present instance. One c.c. of antimeningococcus serum[24] was injected subcutaneously to determine if any hypersensitiveness existed on the part of the patient for this particular serum. As

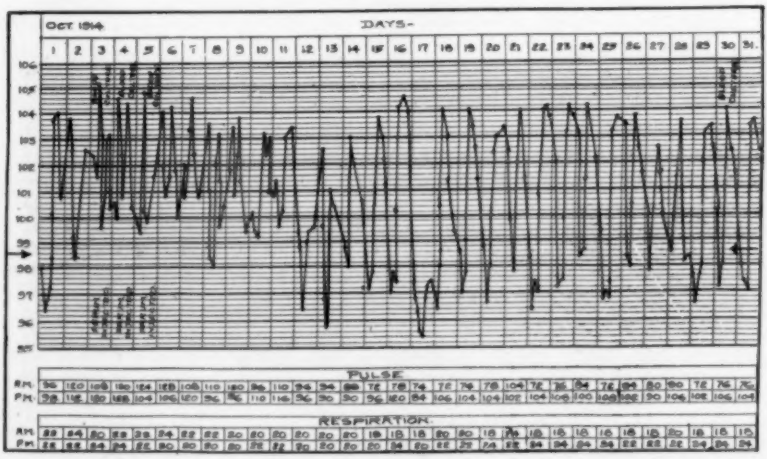


Chart 2.—Patient's pulse, temperature and respiration record during October, 1914.

no local or general reaction followed after four hours, 20 c.c. of the serum were administered intravenously. Before the injection of the serum and in all future administrations, 10 c.c. of the blood were first removed for bacteriologic study. The serum was given entirely by the intravenous method. The patient was alarmed and nervous during the administration of the serum. The temperature rose in a few hours to 105.2 F., the highest since admission.

September 25: The patient asserted that he was decidedly better, and the temperature was lower than for the past few days. A detailed examination of a specimen of deep sputum forwarded to the laboratory on the 24th failed to show the meningococcus and contained no tubercle bacilli. The index finger of the right hand was painful, red and swollen. Antimeningococcus serum, 20 c.c., was administered.

September 26: Serum, 25 c.c., was given. The patient was very nervous during the administration, complained of retrosternal pain following the injec-

24. New York City Board of Health antimeningococcus serum.

tion, and had a slight chill for about twenty minutes. Patient appeared weaker and appetite was much impaired.

September 28: Serum, 35 c.c., was given. Forty-five minutes after the administration a chill of ten minutes duration occurred and was followed by profuse sweating.

September 30: Forty c.c. of serum were given; a chill occurred, followed by profuse sweating.

October 1: The patient was very drowsy and weak, and complained of distressing pain in the legs. Morphin was administered. There was a slight systolic murmur at the apex. Indistinct murmurs were also heard over the pulmonic and aortic regions. The pulse was regular, of fair volume. Swelling of some of the metacarpophalangeal and phalangeal joints of both hands was noted. An urticarial rash over the left elbow and right knee was seen.

October 3: Serum, 40 c.c., was administered. Shortly after the administration of the serum a chill of twenty minutes occurred.

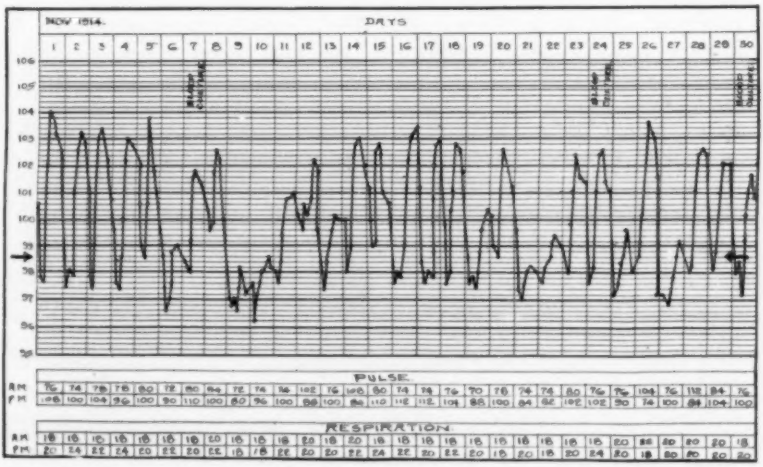


Chart 3.—Patient's pulse, temperature and respiration record during November, 1914.

October 4: Serum, 40 c.c., was given. The injection was followed almost immediately by a rigor, half and hour in duration. The pulse rate increased from 100 to 130. The patient was much prostrated. His arm was slightly swollen and a circumscribed urticarial rash appeared over the site of the previous injection. The swelling and stiffness had lessened in the albows and smaller joints of the hands.

October 5: Serum, 40 c.c., was given. Following the introduction of the serum a marked rigor with collapse occurred, and for a few hours the patient was in a precarious condition. As the last blood culture was reported positive, it appeared advisable, on account of the alarming symptoms that apparently followed the employment of the serum, to discontinue its use.

October 10: Patient felt somewhat better but still complained of exquisite pain in both tibias. A few of the papules on the hands became pustular, but stained smears of their contents and inoculations on Loeffler's serum proved negative.

October 15: The eruption completely disappeared. The heart was free from murmurs.

October 17: Patient was very ill; subnormal morning temperature. Blood pressure: systolic, 92; diastolic, 65.

October 22: Patient was much better. A few fresh papules appeared on the skin. Faint murmur was heard over the mitral and pulmonic areas. No definite rigor occurred since serum was discontinued. No activity in the lung lesion can be detected.

October 30: Fresh papules were usually ushered in with an abrupt rise in temperature. No fresh petechial spots appeared during the past week. A blood culture was taken. Tuberculin O T 0.0001, intracutaneously.

November 2: The tuberculin reaction was positive. The blood culture of October 30 was also positive.

November 7: A blood culture was taken. Severe headache existed for a few hours. The cardiac murmurs were indistinct; the eruption disappearing.

November 15: Eruption had completely disappeared; the appetite was good, the patient much better. There were no cardiac murmurs. The blood culture of November 7 was positive.

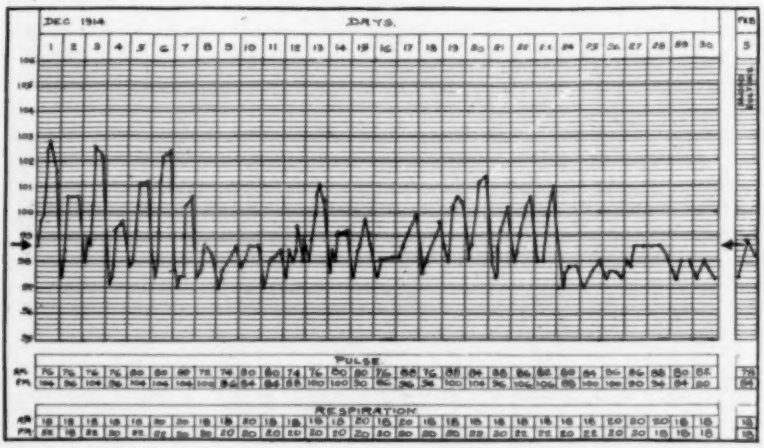


Chart 4.—Patient's pulse, temperature and respiration record during December, 1914.

November 24: No tubercle bacilli were found in the sputum. The improvement was noticeable. A faint systolic murmur was heard at the apex and over the pulmonic area. A blood culture was taken. Blood pressure, systolic 108, diastolic 62.

December 7: Except for slight stiffness in the fingers, there is no evidence of the previous joint involvement. The patient appeared much improved; had gained in weight and the appetite was excellent, but the blood culture of November 30 was reported positive. Convalescence was uninterrupted and rapid. The patient was discharged Jan. 10, 1915. The general condition was good, there were no symptoms, the mitral murmur was indistinct.

Feb. 5, 1915: After a two weeks' convalescent period at home, the patient resumed his former occupation and at present is doing full work. He states that he is feeling very well, has no symptoms and is not unduly fatigued at the end of a day's work. The temperature has remained normal since the date of dis-

charge. His general condition is excellent, his weight 140 pounds. The pulmonary lesion is quiescent; the signs fewer than at any time since the patient has been under observation, and one would be almost inclined to believe, from the results of the examination, that the meningococcus septicemia had had a salutary effect on the pulmonary lesion. The cardiac valves are apparently intact. No murmurs have been detected. The cardiac action is regular, rate 74. The blood culture of February 5 proved negative.

To summarize briefly: The illness extended over a period of more than five months, with a known septicemia of three months' duration. The fifteen blood cultures yielded the meningococcus. The spinal fluid was sterile. The disease was characterized by a septic course, multiform eruption and cardiac murmurs which later disappeared. The course of the infection was apparently not influenced by the administration of the serum.

## BACTERIOLOGY

*Morphology and Staining.*—The organism stains well with the ordinary anilin dyes and is decolorized by the Gram method of staining. In appearance it is biscuit shaped, arranged in diplo or tetrad forms and occasionally in small agglomerations. No chain formation was noted. Marked variation in the size and staining qualities of the organism are observed on the same slide. By Neisser's method of staining, Babes-Ernst bodies cannot be demonstrated.

*Cultural Characteristics.*—Ascitic agar twenty-four-hour growth shows colonies circular, slightly convex, with smooth, fairly distinct outlines. The average diameter of the colonies is 2 mm., but considerable variation of size is observed. The colonies enlarge by continued cultivation. Viewed by reflected light the colonies are gray or grayish white in color and present a smooth, moderately glistening surface. By transmitted light some appear as fairly uniform gray disks; others have a grayish white or faintly yellow center, surrounded by a more or less translucent zone. The growth is somewhat viscid, but is not adherent to the medium.

*Microscopic Appearance.*—Examined with a low power lens, the colonies appear uniformly circular, with an entire or undulating border. The center of the colony is brownish yellow and granular, the periphery is structureless and translucent. On the second or third day, crystalline deposits occur in the granular structure of the colony, which has now become coarser in appearance.

On blood-agar (sheep) the growth is luxuriant. Guinea-pig blood-agar—first transplant—shows a luxuriant growth. Ascitic bouillon shows slight cloudiness with a gradually increasing deposit and pellicle formation. Fragments separate from the pellicle and fall to the bottom. Dextrose agar—first transplant shows scant or no growth. On plain bouillon the younger generations grow more sparsely than on ascitic bouillon. Dextrose calcium carbonate broth gives a luxuriant growth which retains its viability for many weeks at 37 C., with the

formation of a brownish-yellow pigment after the fourth week. On milk growth takes place without producing coagulation. Gelatin shows no growth at room temperature.

Attempts to grow the organism on the above mentioned mediums at room temperature were unsuccessful.

*Carbohydrate Fermentation Reactions.*[25]—Dextrose, +; Maltose, +; Levulose, —; Galactose, —; Lactose, —; Saccharose, —.

*Opsonin Reaction.*—Patient's Serum: Meningococcus (stock) 1:200+; 1:500±; Meningococcus (patient) 1:200+; 1:500—; Parameningococcus 1:20±; 1:50—.

*Agglutination.*—Patient's Strain: Board of Health (New York City) antimeningococcus serum, at 56 C. for twenty-four hours: 1:10++; 1:20++; 1:50++; 1:100+; 1:200—.

Half of a twenty-four hour agar culture injected intraperitoneally kills young guinea-pigs (115 gm.) in twenty-four hours, showing, at necropsy, typical peritonitis similar to that described by Flexner for the meningococcus.

The morphology, growth on ordinary mediums, rapid autolysis in fresh cultures are characteristic of the meningococcus. The pathogenicity and biologic reactions check with the meningococcus.

When the characteristic symptoms of a disease caused by a known specific excitant are wanting, it is quite justifiable to question the identity of the organism isolated unless definite proof is forthcoming that it conforms in all particulars to the specific organism. In the present instance, the bacteriologic data appear sufficient to warrant designating the micro-organism recovered as a true meningococcus.

If one be correct in presuming that the nature of the organism in this case has been satisfactorily established, it is difficult to explain the source of infection, since no reported cases of cerebrospinal fever existed in the neighborhood in which the patient lived for months previous to the onset of the illness. The possibility that direct infection, that is, from person to person, occurred, must, however, be considered, even in the absence of cases of epidemic meningitis, since Kutscher[12] was able to demonstrate the presence of meningococci in the throats of healthy individuals four times, apart from epidemics and when no connection with sporadic cases could be determined. Contact with a meningococcus carrier must therefore be considered a possible source of infection, and the determination in the present case of a meningococcus carrier would have been of decided value in establishing the probable source of infection, but owing to the delay in diagnosis, and also to the fact that the meningococcus is only a temporary resident of the nasopharynx it is very probable that an investigation to determine this point would have resulted in failure.

25. Hiss serum water, + = acid.

The many investigations of the past few years to determine the portal of entry of the meningococcus proved unsuccessful, until the discovery of Albrecht and Ghon[10] that the nasal secretions of patients suffering from epidemic meningitis harbored the meningococcus. This observation was soon confirmed by a number of observers, including Flügge,[26] Kolle and Wassermann[27] and von Lingelsheim.[28]

In the majority of cases of epidemic meningitis the presence of sore throat and the absence of any other focus of infection corroborated the view that the organism gains access to the meninges through the nasopharynx from this point. Westenhöffer[29] makes the statement that every case of epidemic meningitis is first a case of meningococcus pharyngitis. In twenty-nine cases of epidemic meningitis coming to necropsy, he was able to demonstrate an acute pharyngitis in every instance. Meyer[30] in a detailed study of thirty-two cases of this disease found a well-marked inflammation of the nasopharynx in twenty-four. Koplich[31] quotes Goodwin and Sholly to the effect that the organisms can be recovered from the nasal mucus in 50 per cent. of the cases during the first two weeks of the disease, and in 10 per cent. of those who come in contact with patients. It therefore appears fairly well established that the upper respiratory tract is the usual portal of entry for the meningococcus. No evidence of a nasopharyngeal inflammation could be determined in the present case, but this fact would not be sufficient in itself to exclude the nasopharynx as the portal of entry.

The presence of a long-standing lesion of the lung in the present case might reasonably be considered as affording excellent conditions for the entrance of the meningococcus into the body. This view is strengthened by the fact that at necropsy the meningococcus has been reported associated with a pulmonary lesion. The failure in the present instance to demonstrate the intracellular coccus in the sputum or the pharyngeal secretion makes it difficult to state with any degree of certainty the probable channel selected by the meningococcus in gaining access to the blood stream.

Although opinions regarding the portal of entry in epidemic meningitis may be said to be unanimous, the question as to the paths selected by the meningococcus in reaching the brain still remains under discussion. The theory of direct extension, that is, from the nasopharynx by means of the lymphatics, to the meninges of the brain, finds many

26. Flügge: Klin. Jahrb., 1906, xv, No. 2.
27. Kolle and Wassermann: Klin. Jahrb., 1906, xv, No. 2.
28. Von Lingelsheim: Klin. Jahrb., 1906, xv, No. 2.
29. Westenhöffer: Berl. klin. Wchnschr., 1905, xlii, 737.
30. Meyer: Klin. Jahrb., 1906, xv.
31. Koplich: In Osler's Mod. Med., ii, 499.

active exponents, notably Westenhöffer,[32] Meyer[30] and von Lingelsheim.[28] Elser and Huntoon[33] in an exhaustive study of epidemic meningitis, are inclined to favor the blood stream as the avenue selected by the meningococcus in reaching the brain, and summarize the evidence in favor of a hemotogenous origin as follows:

(1) The early generalization of the bacteria as shown by the anatomic findings in individuals who succumb within twenty-four hours; (2) the early appearance of the meningococcus in the blood in some instances, and (3) the simultaneous occurrence of symptoms referable to the brain, and to structures more or less removed from the central nervous system.

To further support this view, they attempted to show that the mode of onset of the disease is incompatible with the assumption that it gains access to the brain by direct extension. They also advance experimental evidence in favor of a hemotogenous mode of infection. The present case would appear to furnish further evidence in favor of the view advanced by Elser and Huntoon.[33]

In view of the relatively few reported cases of primary meningococcus septicemia, it is difficult to determine the value of any of the therapeutic measures employed. The efficacy of antimeningococcus serum in epidemic meningitis suggested that this form of therapy might also prove of value in meningococcus septicemia.

Liebermeister's[21] patient received one intravenous injection of 20 c.c. of Wassermann's serum, but no statement follows concerning the action of the serum on the disease.

Cecil and Soper[19] gave 15 c.c. of Flexner's serum subcutaneously and the following day repeated the dose intravenously. The serious condition of the patient previous to the first injection precludes an opinion of its value in this case. The authors state that the first injection was without effect.

Bovaird[8] administered Flexner's serum four times during a period of five days in a case of meningococcus septicemia with sterile spinal fluid. Twenty c.c. were given intradurally; 25 c.c. intravenously and 60 c.c. subcutaneously. The blood culture before the first injection of the serum and in all subsequent cultures proved sterile. The author believes that it is not justifiable to assume from the fact that the blood proved sterile, that the organism had altogether disappeared from the blood before the introduction of the serum. From clinical observation he concludes that the serum played an important part in the improvement and ultimate recovery of the patient.

32. Westenhöffer: Berl. klin. Wchnschr., 1906, xliii, 1267.
33. Elser and Huntoon: Jour. Med. Research, 1909, xx, 373.

In the present case, 260 c.c. of antimeningococcus serum were administered intravenously during a period of twelve days. The initial dose of 20 c.c. was gradually increased until the maximum of 40 c.c. was reached.

The introduction of the serum was followed in each instance, after a period varying from twenty minutes to a few hours, by an increase in the severity of the symptoms. The presence of an urticarial rash, increase of pain in the joints and rigors with marked prostration conformed in many respects to the symptoms observed in serum sickness.

The severity of symptoms, together with the fact that the blood cultures still remained positive, suggested the advisability of discontinuing this form of treatment.

It must not be inferred, however, from our experience, that antimeningococcus serum might not be an available form of therapy in this type of case. The established chronicity of the disease before the employment of the serum, selection of dose and time interval between the injections might prove to be the deciding factors in explaining the conduct of the serum in our hands.

In the absence of any well-defined focal lesion, and in view of the protracted nature of the illness, the term "chronic meningococcus septicemia" would appear appropriate in designating the condition in the present instance. The case reported by Liebermeister is strikingly similar to the present case in the chronicity of the disease, the presence of a multiform eruption appearing in successive crops, multiple arthritis without the formation of an exudate, and associated with muscular contraction, moderate leukocytosis, and a septic type of fever. Liebermeister suggests that the above symptoms enable one to determine the accessory symptoms of meningitis; that is, those due to the general infection and not to the focal lesion.

I have been unable after a rather careful review of the literature to discover any mention of meningococcus septicemia associated with clinical pulmonary tuberculosis, and it would be hazardous on the basis of a single case to formulate any definite conclusions regarding the behavior of the pulmonary lesion in the presence of this type of septicemia. One would expect that any disorder characterized by a protracted and septic course, associated with an extreme degree of emaciation, would exert a harmful influence on the pulmonary condition. However, a study of the signs and local symptoms indicate that apparently no activity in the pulmonary lesion has occurred. The patient retained the allergic state, reacting moderately to an intracutaneous injection of 0.0001 c.c. of original tuberculin, which might throw some

light on the question as to why the pulmonary condition in the present instance did not suffer.

In conclusion, the presence or absence of an accompanying meningitis in the present case is a question that must fail of absolute solution since postmortem examination is the final word in its establishment.

I wish to express my thanks to the medical staff for many helpful suggestions, to Dr. S. Flexner, Dr. M. Wollstein and Dr. O. T. Avery for performing the serologic tests and checking the bacteriologic work; to Dr. A. McNeil of the Department of Health, New York City, for the fixation test for gonococcal infection and to Mr. M. Morita for invaluable aid in carrying out the bacteriologic and other laboratory tests.

# TREATMENT OF CYSTINURIA

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Cystinuria is a rare but very interesting disease. Its chief interest is from the point of view of body metabolism and the various careful studies of this disease have added much to our knowledge of protein katabolism. The treatment of the disease has received but little consideration.

Cystinuria has a definite symptom-complex and may be readily diagnosed. The symptoms are those of renal stone, and differ but little from those of other types of renal-stone disease. Certain features, however, are somewhat characteristic.

1. The stones are usually very small. They are sharp edged, rough, with a color and texture very similar to that of a small piece of maple sugar.

2. The stones tend to occur in the urine in showers, usually after a period of high protein ingestion.

3. The amount of blood in the urine is often out of proportion to the symptoms and to the size and number of stones.

The diagnosis of cystinuria is readily made by microscopic examination of the urine. Cystin appears in the form of flat hexagonal crystals. These are insoluble in weak acids, but are readily soluble in weak alkalies.

The treatment has been almost entirely dietary. Alsberg and Folin[1] in a striking piece of work, proved that the amount of cystin excreted in the urine, in a case of cystinuria, varied directly with the amount of protein consumed. They do not believe that there are different degrees of severity of the disease but that the amount of cystin excreted depends on the amount of protein consumed, plus the protein katabolized from the wear and tear on body tissues. For this reason it is not possible to get the urine of a cystinuric free from crystals. On a diet which contained practically no protein, the amount of cystin excreted was very small. At the end of thirteen days, however, the patient was not cystin-free.

The practical application of these facts in the treatment of cystinuria is self-evident. The patients should be kept on a low nitrogenous

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1. Alsberg and Folin: Am. Jour. Physiol., 1905, xiv, 54.

diet. In the subsequent treatment of their patient, Folin was able by these means, to keep him free from symptoms for over a year. Most patients, however, chafe under the restrictions of a low protein diet, and are willing even to suffer from renal colic, rather than bear the monotony of the nitrogen-poor regimen. Furthermore 30 to 50 gm. of protein a day is minimum for normal metabolism, and this amount causes a considerable excretion of cystin.

Cystin is so readily soluble in weak alkali, that it seemed plausible to treat cystinuria by the addition of sodium bicarbonate to the diet. This empirical treatment only needed a patient for its justification. Curiously enough two of these cases were studied at about the same time and treated by the same method, one by Klemperer and Jacoby[2] in Berlin and one by myself. The report of Klemperer's case, however, was published in March, 1914, and since this treatment was similar to mine, though my conclusions are at variance from his, it was thought advisable to defer publishing my studies for a year, meanwhile keeping the patient under observation.

Klemperer's patient had a typical history and symptom-complex. The studies are briefly reported. The patient was first placed on a rich protein diet. No estimation of the nitrogen intake or of the urinary nitrogen is recorded. The cystin both precipitated and in solution was determined by Gaskell's[3] method. They found a total of 716 mg. of cystin on the fifth day of the high protein diet.

The patient was then put on a very low protein diet for three days. The average excretion of cystin was 78 mg. This they called the "endogenous cystin." Finally a mixed diet was given. The nitrogen intake or excretion is not stated. From 6 to 10 gm. of sodium bicarbonate were added to the diet each day. The cystin both in the precipitate and in solution rapidly decreased and on the fifth day none was present in the urine. These results are very striking, and their conclusions are that the alkali does not act as a solvent for cystin, but actually influences metabolism of the body so that cystin is not excreted or even formed.

The patient studied by us had a characteristic history.

Patient 812, a white printer, unmarried, aged 22, was entered as complaining of gravel present in the urine for twenty months.

*Family History.*—The patient's father is living and is said to have tabes dorsalis. His mother, one brother and three sisters are living and well. No tuberculosis, cancer, diabetes or kidney trouble occur in the family. He denies venereal disease. He uses a moderate amount of tea, coffee and tobacco, but no alcohol.

*Past History.*—Patient's health has always been poor. He had scarlet fever with a cardiac complication at an early age. At 8 years of age he had rheumatic

2. Klemperer and Jacoby: Therap. d. Gegenw., 1914, lv, 101.
3. Gaskell, J. F.: Jour. Physiol., London, 1907, xxxvi, 142.

fever and chorea and was ill for eight or nine months. Rheumatic fever recurred every spring for two or three years. Two years ago he was operated on at the Boston City Hospital for appendicitis and inguinal hernia and made a satisfactory convalescence.

*Present Illness.*—Six months after the operation the patient passed a small stone in the urine. This was soon followed by many others. Several patent medicines were tried, without relief. In August, 1913, the patient went to the Boston City Hospital with complete anuria, which he said had existed for three days. He was in the hospital three days, during which time he passed no urine. Being of a stubborn and intractable disposition, he refused cystoscopy or operation. He was discharged against advice and walked home. On the journey, "something gave way" and during the day he passed over "a gallon" of urine. The patient was seen by us first in January, 1913, when he came to the Peter Bent Brigham Hospital outdoor department. His chief symptoms then were pain in the lower lumbar region, pain over the symphysis pubis and blood and gravel in the urine.

*Physical Examination.*—The patient's weight was 110 pounds; he was poorly developed, though fairly well nourished. The heart was slightly hypertrophied, with a high-pitched systolic murmur at the apex. The abdomen showed slight tenderness in the costovertebral angle on both sides. No abdominal masses or tenderness were made out. Examination otherwise was negative. The urine showed large numbers of typical cystin crystals and a small amount of blood, but no casts. Blood pressure was normal, hemoglobin, 95 per cent., and white blood cell count, 10,000.

The patient was admitted to the house for metabolic study Jan. 31, 1914. The following data was recorded: intake of fluid, intake of nitrogen, output of urine, specific gravity of urine, the reaction of the urine as measured by the hydrogen ionization method, output of total nitrogen, urea, uric acid, ammonia, total sulphates and inorganic sulphates. (The results are shown in the table.)

The hydrogen ionization was determined according to the colorimetric method of Henderson and Palmer.[4] The factor 7.4 represents the reaction point of blood, the most alkaline figure, 8.4, is definitely pink to phenolphthalein. The diet was standardized by Locke's[5] tables. The urinary nitrogen, urea, uric acid and ammonia were determined by the microchemical methods of Folin[6] and his associates. The total sulphates and inorganic sulphates were determined by the method of Folin.

Alsberg and Folin[1] have shown that cystin is best quantitated by the determination of neutral sulphur. Ethereal sulphur was not determined since it remains constant. On 119 gm. protein intake the normal average excretion of ethereal sulphur as $SO_3$ is 0.22 gm. in twenty-four hours. The normal average of neutral sulphur as $SO_3$ is 0.17 gm. In cystinuria there is a marked increase in the neutral sulphur, which is due to the sulphur of cystin.

The patient was put on a standard diet containing 10.5 gm. of nitrogen. He remained on this diet two days before the records were begun. His blood examination showed:

| | |
|---|---|
| Nonprotein nitrogen ..... | 28.0 mg. per 100 c.c. of blood |
| Urea nitrogen ..... | 14.0 mg. per 100 c.c. of blood |
| Uric acid ..... | 1.4 mg. per 100 c.c. of blood |
| Creatinin ..... | 1.2 mg. per 100 c.c. of blood |
| Creatin ..... | 10.0 mg. per 100 c.c. of blood |

The creatinin and creatin determinations were made by Dr. W. Denis.

On February 5, 2 gm. of cystin were given to the patient. This was excreted at once as inorganic sulphur, substantiating the observation of Alsberg and Folin,

4. Henderson and Palmer: Jour. Biol. Chem., 1912, xiii, 363.
5. Locke: Food Values, New York, D. Appleton & Co., 1911.
6. Folin, O.: Jour. Biol. Chem., 1912, xi, 493.

RESULTS OF URINE EXAMINATION IN PATIENT WITH CYSTINURIA

| Date | Intake Fluid, c.c. | Volume Urine, c.c. | Sp. Gr. | Hydrogen Ioniz. | Total Nitrogen, Gm. | | Urea N | Ammonia N | Uric Acid | Total Sulphur as $SO_3$ | Inorganic $SO_3$ | Undetermined $SO_3$ | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Intake | Output | | | | | | | |
| 2/3/14 | 2,000 | 710 | 1.023 | 7.3 | 10.5 | 10.56 | 8.02 | 0.334 | 0.72 | 1.78 | 1.14 | 0.64 | Standard diet |
| 2/4/14 | 1,950 | 1,020 | 1.020 | 7.4 | 10.5 | 11.52 | 8.68 | 0.234 | 0.50 | 1.89 | 1.19 | 0.69 | Standard diet |
| 2/5/14 | 1,650 | 810 | 1.023 | 7.2 | 10.5 | 10.87 | 8.78 | 0.319 | 0.31 | 2.73 | 1.98 | 0.75 | Plus 2 gm. cystin. |
| 2/6/14 | 2,100 | 970 | 1.020 | 7.2 | 10.5 | 10.24 | 8.09 | 0.313 | 0.45 | 1.70 | 1.09 | 0.61 | Standard diet |
| 2/7/14 | 1,900 | 1,550 | 1.024 | 8.2 | 10.5 | 10.47 | 9.39 | 0.540 | 0.86 | 1.98 | 1.08 | 0.90 | Standard diet and 40 gm. sodium bicarbonate |
| 2/8/14 | 1,750 | 1,680 | 1.021 | 8.4 | 10.5 | 9.50 | 8.10 | 0.506 | 0.55 | 1.64 | 0.907 | 0.73 | Standard diet and 40 gm. sodium bicarbonate |

that cystin is katabolized, and not absorbed and excreted unchanged. On the 7th, 40 gm. of sodium bicarbonate were added to the diet. This was repeated on the 8th. This treatment was followed by a slight increase in the neutral cystin sulphur, rather than a decrease, as noted by Klemperer. The striking thing that occurred, however, was that despite the increase in cystin sulphur, cystin crystals at once disappeared from the urine. This could be due to but one thing, namely, alkalinity of the urine.

Klemperer states that in his case cystin disappeared from the urine both in the precipitate and in solution; in our case the cystin simply went into solution. It seems hardly reasonable to suppose that sodium bicarbonate can influence body metabolism since Henderson[7] has shown that even very large amounts of alkali added to the blood do not influence its reaction. It has been suggested that in Klemperer's case, the cystin was present in the urine, but was in solution, and the method used did not detect it in the presence of the alkali.

The results from giving 40 gm. of sodium bicarbonate were definite and satisfactory, but needless to say, a patient cannot take 40 gm. nor even 10 gm. of sodium bicarbonate every day without digestive and other disturbances. In a previous unpublished experiment on hydrogen ionization of the urine, we have found that it required from 8 to 12 gm. of sodium bicarbonate a day to keep the urine definitely alkaline, that is, below 7.4, when on a diet of from 10 to 12 gm. of nitrogen. The higher the total nitrogen, the more alkali required. The practical solution is obvious; a low nitrogen diet which will offer some variety, with small amounts of sodium bicarbonate to keep the urine alkaline.

Our patient declined to tolerate any further quantitative metabolic experiments, but it has been possible to follow him clinically. He was put on a 5 to 6 gm. nitrogen diet with 4 gm. of sodium bicarbonate a day, given some litmus paper and told to keep the urine at a point where the litmus always turned blue.

*Subsequent History.*—The patient reported at frequent intervals. Whereas he had been having all the symptoms of renal stones; colic, constant pain in the back radiating down to the groin, hematuria, etc., he was now entirely free from these symptoms. An occasional crystal could be found in the urinary sediment. He passed no stones until August when he broke his strict dietary rules eating large amounts of meat and fish. He passed 20 or 30 stones within two or three days, and suffered considerable pain and distress.

Following this period it was thought best to give the patient one protein day a week. The low nitrogen diet was taken every day but Friday. On this day he was given 10 or 12 gm. nitrogen together with from 12 to 14 gm. of sodium bicarbonate. The patient was better satisfied and free from symptoms.

In February, 1915, one year after the metabolic studies had been made, the patient was given 10 or 12 gm. of nitrogen a day for one week, without sodium bicarbonate. At the end of three days there was a return of all symptoms, with the passage of 50 to 75 small stones and showers of typical crystals in the urine.

The patient was then put on the regimen suggested by Klemperer, 10 to 14 gm. of nitrogen a day with 10 gm. of sodium bicarbonate a day. At the end of two weeks, cystin crystals were readily found in the urine, and an occasional small stone was passed; furthermore the large doses of bicarbonate were not well tolerated by the stomach. He voluntarily returned to the regimen of six low protein days and one moderate protein day. Beginning March 2, 1915, he was given a diet containing 10 to 12 gm. of nitrogen and 12 to 15 gm. of sodium bicarbonate. After five days the urine was found to be alkaline to litmus, with only an occasional cystin crystal in the sediment. Total cystin determined by a new colorimetric method in Dr. Folin's laboratory showed 0.6 to 0.7 gm. of cystin. This experiment furnishes conclusive evidence, that in our case at least, cystin is being excreted in such an amount as would be expected from the nitrogen intake, but is rendered soluble by the alkali.

7. Henderson, L. J.: Jour. Biol. Chem., 1909, vi, 29.

## CONCLUSIONS

1. Cystinuria is best treated by a low protein diet, with the addition of sufficient alkali to keep the urine alkaline.

2. Cystin crystals will practically disappear from the urine of a cystinuric when sufficient sodium bicarbonate is added to the diet to render the urine alkaline.

3. The amount of sodium bicarbonate necessary to render the urine alkaline, when the patient is on a nitrogen intake of 10 gm., or more, is greater than can be well borne by the stomach.

4. Sodium bicarbonate does not influence body metabolism in cystinuria but simply renders the cystin soluble.

I desire to thank Dr. Folin for his many helpful suggestions in this study.